THE FEMALE PROSTATE *
BLADDER-NECK OBSTRUCTION IN WOMEN

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ALTHOUGH hardly recognised in this country, bladder-neck obstruction in women is a very real condition which is not so very uncommon. In a previous communication I described eleven cases (Moore 1952). This paper is based upon thirty-three of the cases encountered since 1948. Not infrequently the wife of one of my prostatic patients has said to me, "I am sure I have the same trouble myself, I have just the same symptoms." Sometimes this diagnosis has been correct. In one family I have removed a grandfather's prostate, his son's, and his daughter-in-law's, all with equally good results!

The bladder neck is the junction between the bladder and the urethra. The circular muscle of the latter normally holds it closed, and only when this junction is open can micturition occur. Many now regard the urethra and the bladder in the female, and the bladder and the posterior urethra in the male, as one viscus. They are certainly intimately related in function, and minor changes at the junction between them can lead to gross interference with micturition. It is generally known that the detrusor muscle of the bladder is continued into the proximal urethra. There is also a large body of muscle posteriorly under the trigone, partly derived from ureteric muscle which enters into the posterior urethra. When micturition occurs, contraction of the detrusor muscle leads to shortening of the urethra and pulling open of the sphincter muscle at the bladder neck (fig. 1). This mechanism can be demonstrated by the study of cystourethrograms taken at different phases of micturition, by cineradiography using the image intensifier, and also by endoscopy itself. From my own observations I have no doubt that the female bladder neck usually opens more easily than in the male, and opens in the entire circumference of the orifice whereas in the male it is mostly the posterior quadrant which moves. This difference in function of the bladder neck in the two sexes is associated with the more rigid nature of the structures round the bladder neck in the male and explains the higher incidence of bladder-neck obstruction in that sex.

Any thickening or rigidity of the bladder neck in the female will make it more difficult for the muscles of the bladder to pull it open. Obstruction is then present. The factors which can be responsible for this loss of flexibility can be inflammatory, consisting of œdema, cellular infiltration, and fibrous-tissue formation; glandular hyperplasia; internal-sphincter hypertrophy, or, in rare cases, neoplastic change.

The female urethra is surrounded by very many glands (fig. 2). Many believe that these represent the homologue of the prostate in the male. Several workers, Folsom (1931) and Young (1940) particularly, have been impressed by the similarity of the tissue excised from the bladder neck in the female to that of the prostate in the male, and have regarded the condition as the female prostate. There is no doubt that the prostate is under hormonal control and it may well be that the female urethral glands are too. Young (1940) described a case of adrenal virilism in the female in which hypertrophy of these glands was such that to the naked eye the structure below the bladder neck

* Based upon a lecture given to the section of surgery of the Manchester Medical Society on Feb. 10, 1959.

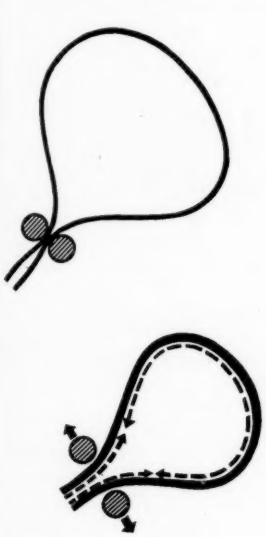

Fig. 1—Schematic representation showing how contraction of the detrusor muscle of the bladder causes shortening of the urethra and opening of the bladder neck.

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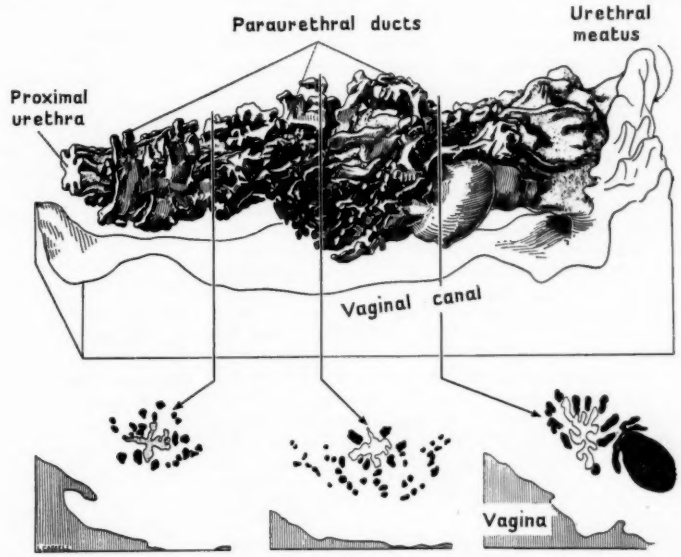

Fig. 2—Wax model representation of the urethra showing paraurethral glands. (Huffman, J. W. *A.M.A. Arch. Surg.* 1951, 62, 615.) Reproduced by kind permission of the author and publishers.

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resembled the prostate. The condition is certainly commonest in the prostatic age-group. In my cases, however, the tissue excised from the bladder neck has not really simulated a true prostatic adenoma. The common findings have been squamous metaplasia of the epithelial lining of the bladder neck and infiltration with inflammatory cells, œdema, or fibrosis. In one case there appeared to be hypertrophy of the internal sphincter. All this patient's reactions were slow and we postulated there was some neuromuscular dysfunction at the bladder neck leading to hypertrophy of the internal sphincter. Obstruction at the bladder neck causes hypertrophy of the detrusor muscle which may still be able to empty the bladder completely. Then, as decompensation of bladder function occurs, increasing amounts of residual urine remain after each micturition. Finally chronic retention ensues and the ureters become dilated and associated with hydronephrosis and renal insufficiency. In addition the urinary stagnation encourages infection with all the associated dire possibilities.

Relation of Bladder-neck Obstruction to Cystocele

As it is, unfortunately, still traditional for urinary symptoms in the female to lead to a gynæcological consultation, I must discuss the relation of bladder-neck obstruction to cystocele.

In my view cystocele and uterine prolapse per se are not the cause of urinary difficulty; nor is there any reason why they should be. The bladder is a powerful muscular organ which will contract even when isolated from the body. Recently I encountered a patient with an extreme degree of uterine prolapse and cystocele without any urinary symptoms of any kind.

As cystocele is a comparatively common condition it is often operated upon in the belief that it is the cause of the urinary symptoms. In my experience these are rarely, if ever, cured thereby. Colporrhaphy must be associated with much postoperative fibrosis. That which occurs round the bladder neck may render it difficult to open and cause urinary obstruction. Thus the urinary symptoms whatever their cause may be made worse. When, as sometimes happens, an undiagnosed bladder-neck obstruction was present originally, the final condition is much worse than the first, residual urine increases, the cystocele recurs, and further operation is carried out. There were six such cases in the present series.

Mrs. A, aged 76.—Complaining of difficulty of micturition for 50 years, since the birth of her first child. Had colporrhaphy and amputation of cervix 28 years ago. Symptoms of urinary difficulty persisted and another colporrhaphy was carried out in 1957. Afterwards seen by me and found to have residual urine of 30 oz. I had no doubt she had been suffering from chronic retention of urine for many years. Endoscopy showed marked swelling of the tissue round the bladder neck, which was projecting into the urethra like prostatic lobes. The bladder was very trabeculated. A transurethral resection of the bladder neck was carried out and 2 g. removed. Histological report of the excised tissue showed hyperplastic but regular transitional epithelium with fragments of smooth muscle. There was considerable infiltration of the submucosa with lymphocytes, eosinophils, and plasma cells. Patient had urethral catheter drainage for 5 days. Has since passed urine without any difficulty, and now, 18 months later, the residual urine is only 3 oz.

I believe such misdiagnosis is common. Colporrhaphy can, of course, also cause urethral stricture, of which I have seen several examples; but none are included in this series, which are of bladder-neck obstruction only.

Postoperative Retention

As in the male sex, a patient with well-compensated bladder-neck obstruction may develop retention of urine on being confined to bed. Thus, in my series, three cases occurred after operation (one herniorrhaphy and two cataract operations) whilst one patient was suffering from a fractured neck of the femur and two from severe rheumatoid arthritis. Moore (1952) suggested that postoperative cases should be avoided by more care in preoperative diagnosis, so that the associated bladder-neck obstruction is recognised, and dealt with at the same time as the original lesion.

Clinical Features

Essentially these patients complain of difficulty in micturition, which, as in the male, comprises difficulty in starting the act, particularly when the bladder is full, and a lack of force in the flow. As residual urine increases in amount, frequency of micturition becomes troublesome. Sometimes secondary infection leads to dysuria, frequency, and, occasionally, hæmaturia. Renal obstruction may even be such that uræmia develops.

I have divided my cases into the following clinical types:

1. Difficulty of micturition	6 (9)	6. Hæmaturia	3 (5)
2. Acute retention	4 (8)	7. Uræmia	2 (3)
3. Chronic retention	7 (7)	8. Postoperative retention	3 (3)
4. Chronic retention with incontinence	3 (6)	9. Enuresis	2 (6)
5. Cystitis	3 (23)	10. Abdominal tumour	0 (15)

This clinical classification is based on the presenting symptom, but most cases also had other symptoms. The figures in parentheses relate the total number of patients in the series having each separate symptom.

A familiarity with diseases of the urinary tract in the female has protected me from mistaking the chronically distended bladder for an abdominal tumour. Trafford (1959) recently described such a case as an example of atony of the bladder. Occasionally in both sexes patients with definite urinary obstruction do not appreciate the change in micturition which has taken place, and their presenting symptom may be that of abdominal swelling. In the male I have encountered this three or four times; but in this series of females there was no such case.

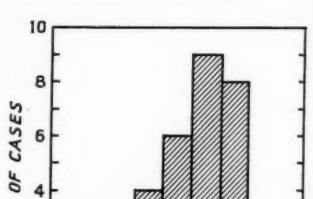

Fig. 3—Age incidence of bladder-neck obstruction in the female in 33 cases.

The age incidence is interesting (fig. 3), varying from 20 to 84 years. The condition is most common in the prostatic age-groups, 50, 60, and 70 years. Six patients were unmarried.

Diagnosis

The diagnosis is missed more often through lack of knowledge of the occurrence of urinary obstruction in the female than through carelessness in clinical examination.

As in the male, most of the symptoms of urological disease can be primarily caused by a bladder-neck obstruction. Thus, although chronic retention may be obvious, the distended bladder may be mistaken for an ovarian cyst (Trafford 1959). With awareness of the

Fig. 4—Patient, aged 31, with chronic retention of urine due to bladder-neck obstruction. Intravenous cystogram taken after micturition, showing residual urine.

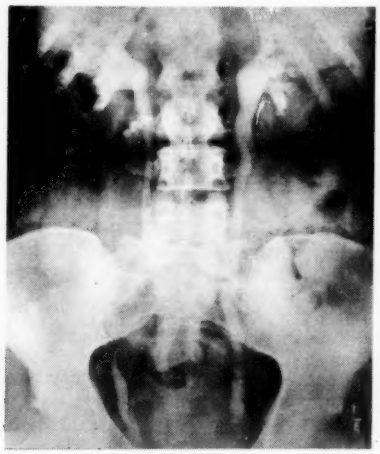

Fig. 5—Same patient. Intravenous urogram showing dilatation of both ureters and pelves.

Fig. 6—Same patient. Intravenous urogram showing disappearance of ureteric and pelvic dilatation after transurethral resection of bladder neck.

occurrence of urinary obstruction in the female, the diagnosis in such cases (groups 2 and 3) is obvious. More often it must be demonstrated by detailed investigation. Estimation of the amount of residual urine—by bimanual examination, urethral catheterisation, and/or intravenous cystography after micturition—is essential (fig. 4). Renal dysfunction (fig. 5) and urinary infection are demonstrated by the usual methods. Cystourethroscopy is the most important procedure. As the instrument is passed along the urethra, a ledge may be felt at the bladder neck. On inspection a prominent lip can be seen in the posterior quadrant—as a median bar, or forming a collar round the bladder neck. Occasionally hypertrophied glandular tissue may bulge into the urethra, like prostatic lobes. The mucosa covering the bladder neck in some cases is white and rigid; more often, as is so common in the female urethra, it is swollen, œdematous, and polypoid. These latter changes are not associated per se with obstruction, but are due to concomitant longstanding inflammatory change in the urethra or are caused by inlying urethral catheter.

In no case have I been able to appreciate any thickening on palpation of the bladder neck against the pubes or the cystoscope. It is not uncommon, however, to feel thickening in the urethra itself, from associated chronic inflammatory changes or previous operation. On one occasion changes seen suggested carcinoma, and this was subsequently confirmed.

The most important examination is inspection of the bladder neck under local anæsthesia. Normally during attempted micturition one can see that all quadrants of the bladder neck will move proximally and laterally. In patients with severe bladder-neck obstruction no movement at all will take place, and with various degrees of obstruction various limitations of the excursion of the bladder neck can be appreciated.

Differential Diagnosis

One must exclude other causes of urinary obstruction—namely, mechanical obstruction of urethra, neurogenic lesions, and hysteria.

Mechanical Obstruction of Urethra

The causes of mechanical obstruction are:

1. *From above*
   - Vesical calculi
   - Pedunculated vesical tumours
   - Ureterocele
   - Diverticulum of bladder
2. *In urethra*
   - In lumen:
     - Stone
     - Foreign body
     - Valves and diaphragms
     - Ureterocele of ectopic ureteric orifice
   - In wall:
     - Stricture (posttraumatic, postinfective and malignant)
     - Diverticulum
     - Abscess of urethral gland
   - Outside wall:
     - Fibroids of body of uterus impacted in pouch of Douglas
     - Ovarian cyst impacted in pouch of Douglas
     - Retroverted gravid uterus.
     - Carcinoma of cervix
     - Fibroids of cervical canal.

All these lesions can be easily identified by careful clinical examination combined with radiological and endoscopic examination where necessary. Lesions of the uterus do not cause urethral obstruction directly unless they arise from the cervix, when, as they enlarge, they stretch and compress the urethra. The same effect can be caused by mobile swellings of the uterus itself or of the ovaries when they are sufficiently large and become impacted in the pouch of Douglas. Thus, a fibroid of the body of the uterus, or an ovarian cyst which is freely mobile in the abdominal cavity, cannot be the cause of retention of urine.

Neurogenic Lesions

In every case one must suspect a neurogenic cause. Many of my cases, and all in which there has been any doubt, have been seen by a neurologist. Usually it is quite clear when any organic nerve lesion is present. Occasionally the presence of a concomitant disease, which could possibly involve the bladder innervation, makes diagnosis extremely difficult, and one may be in doubt whether the obstruction at the bladder neck is primary or secondary to a neurological lesion. When much residual urine is present in a case of neurogenic bladder, transurethral resection of the bladder neck is often the most satisfactory method of therapy. When, therefore, such

a case is mistaken for primary bladder-neck obstruction no great harm has been done. The result in such cases, however, is not as good as in those with primary bladder-neck obstruction.

In one of my cases of neurogenic bladder the early clinical findings were very difficult to assess and a transurethral resection of the bladder neck was carried out to relieve what was thought to be a case of primary bladder-neck obstruction with a moderate residual urine. The immediate result was very satisfactory; but, during the three years which have since elapsed, it has become apparent that the patient has disseminated sclerosis affecting particularly her lower limbs and bladder. The transurethral resection, however, has done no harm and has ensured that the amount of residual urine present is as small as possible.

In another case the immediate result was very unsatisfactory and a large amount of residual urine remained. As this patient had also Paget's disease of the spine, one wondered whether some secondary effect on the bladder innervation was really the cause of the urinary difficulty. However, after four transurethral resections the patient is now symptom-free and the residual urine has been abolished.

A patient suffering from diabetes with a raised cerebro-spinal-fluid protein was completely cured after a transurethral resection of the bladder neck.

Hysteria

Hysteria is the hardest condition to exclude. I do not deny that sometimes it is the cause of urinary difficulty, but I believe that many of these patients are really suffering from bladder-neck obstruction. This is confirmed by the trabeculated bladder and the definite obstructive changes at the bladder neck. When such changes are present transurethral resection can be recommended with confidence.

Miss B, a nurse aged 20, complained of enuresis. She had been seen by many psychiatrists. Investigations showed a much trabeculated bladder with a primary bladder-neck obstruction. The residual urine, estimated on several occasions, was 10 oz. Transurethral resection of the bladder neck was carried out with excellent result. No residual urine and no further enuresis.

Another condition which I have not mentioned and of which I have had no experience is primary atony of the bladder. Trafford (1959) reported four cases. It is very difficult to be sure of this condition. It is not unlikely that in the reported cases minor changes at the bladder neck causing chronic retention have been missed. To the uninitiated the obstructive lesion is very hard to diagnose, and very little change at the bladder neck can cause severe obstruction. It is really astonishing sometimes how little has to be done to the bladder neck to put things right. Occasionally, when the residual urine has remained high after transurethral resection, I have wondered whether the primary lesion has not been atony of the bladder. Biopsy, however, has never confirmed that there was anything wrong with the bladder muscle per se. These cases are really examples of secondary atony of the bladder following long-continued distension.

Unrelated Diseases Present

Concomitant diseases have been:

Holmes-Aidie syndrome	1	Hysteria	1
Solitary cyst of kidney	1	Fractured neck of femur	1
Rheumatoid arthritis	2	Papilloma of bladder	1
Paget's disease of spine	2	Uterine fibroid	1
Colporrhaphy	6	Abdominoperineal excision	1
Hypertension	2	Diabetes	1

There are two ways in which these are important. Firstly, as already mentioned, some may possibly be responsible for neurogenic lesions, which may account for the bladder symptoms. In none of the cases in this series, however, was there any such effect. Secondly, others may precipitate the onset of retention of urine. This happened after an abdominoperineal excision of the rectum in one patient and required treatment, just as in the male the prostate often requires treatment in such circumstances. In other patients injury, disease, or operation led to confinement to bed with exacerbation of previously slight symptoms of primary bladder-neck obstruction.

Treatment

Of the thirty-three cases four were treated conservatively and twenty-nine by transurethral resection of the bladder neck.

When obstruction causes severe renal dysfunction, preoperative treatment by indwelling urethral catheter may be necessary. In severe secondary infections a few days' administration of the appropriate antibiotic or sulphonamide, with catheter drainage, will make operation safer. Not all cases require operation. Thus four patients who had very definite obstruction (proved by complete investigation) recovered urinary function after a short period on catheter drainage: the residual urine was not large and operation was not carried out. These patients have been under observation for several years and so far none has required any further treatment, though they may do so some day. Such a state of affairs is exactly comparable to that in the male where the bladder-neck lesion often responds to conservative measures, and no further action is necessary beyond careful observation. Where there is definite residual urine, however, and of course where retention is present, treatment must obviously be undertaken.

In resecting the bladder neck I use a Thompson punch. This is an excellent instrument but must be used with even greater care in the female than in the male, because the distance between the urethra and the vagina is so small. I take great care to remove bites no more than 1 cm. long, and with a finger in the vagina I can judge the depth of cut in the posterior quadrant. Where changes are right round the bladder neck, resections are made circumferentially. The amount has varied between 1 and 2 g. It is astonishing in some cases, however, how little has to be done. In the great majority one resection has put the patient right; one patient required two, another three, and another four resections.

Postoperative Complications

A vesicovaginal fistula may be formed by cutting too deeply, or later by using too much diathermy in securing hæmostasis. Incontinence of urine is due to cutting too distally in the urethra, and likewise can be avoided by care. The only other complications are associated with urinary infection, which is usually present before operation. A satisfactory resection and the appropriate antibiotic are the best means of overcoming it.

Results

In thirty of the thirty-three cases the results were good. Of the four cases treated conservatively, all are doing well so far. Of the twenty-nine treated by transurethral resection, twenty-six have been relieved of the symptoms of urinary obstruction, while residual urine has been reduced or abolished and urinary infection has been overcome (fig. 6). For a few days after the catheter is taken out, many patients have slight incontinence; but this soon disappears. After the resection the bladder is

usually drained with an indwelling urethral catheter for 5 days. When, however, the patient has had a large residual urine for many years it is of course impossible for the bladder to recover tone in this short time. In long-standing cases, therefore, the catheter has often had to be replaced and left for varying periods, and afterwards the residual urine has often had to be checked daily until the bladder muscle eventually recovered. Occasionally in the male sex where there is gross secondary atony with a very large residual urine which does not diminish after long-continued drainage it may be necessary to carry out a partial cystectomy to reduce bladder capacity and increase intravesical pressure and sensitivity. I have not yet seen such a case in a woman, but such therapy might occasionally be required.

One patient suffering from a carcinoma of the bladder neck had to be treated surgically.

In two cases results have been poor. One was an old lady of 78 in whom I caused a vesicovaginal fistula; this was repaired by operation. She made satisfactory progress but died eventually from ascending urinary infection. The second case illustrates the difficulties that may be encountered:

Mrs. C, aged 62. Previous history of failed colporrhaphy for stress incontinence. Admitted to hospital in uræmia—very thin and emaciated. Blood-urea 83 mg. per 100 ml. Intravenous urography showed considerable dilatation of both pelves and ureters. Urine contained numerous white blood-cells with a moderate growth of *Escherichia coli* on culture. With catheter drainage, condition improved remarkably. Investigations showed large residual urine and obstruction at the bladder neck. Transurethral resection relieved obstruction and abolished residual urine. Normal control of micturition except she still had stress incontinence. Gynæcological opinion sought and further colporrhaphy performed. After this she developed total incontinence of urine!

Some time later, in an attempt to cure the incontinence, I carried out a urethral-sling operation without success. Eventually, because she was in such a miserable state, an ileal conduit had to be made. With this, her general condition improved and the conduit was satisfactory. She still, however, was a very poor soul and complained of vaginal discharge. After long-continued gynæcological treatment, this did not clear up, and eventually it was found that the discharge was really coming from her infected bladder. As this did not clear up after prolonged continuous irrigation through a two-way indwelling catheter, the bladder finally had to be removed. It was just an abscess cavity. After this the patient's condition improved and she was discharged home.

Later she had the misfortune to fall and break her femur. After many months in hospital she was discharged home in fair condition, only to contract bronchopneumonia, from which she died.

Summary

Bladder-neck obstruction in the female is a very real condition, just as definite as prostatic obstruction in the male. It can cause many types of urinary symptoms and may lead to severe renal dysfunction. A well-performed transurethral resection not only relieves symptoms but restores the urinary tract to a healthy state.

I should like to record my indebtedness to Dr. G. W. Ollerenshaw and the members of the department of medical illustration at the Manchester Royal Infirmary for their help in the preparation of the illustrations; also to Dr. J. W. Huffman and the American Medical Association for allowing me to reproduce fig. 2.

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ANTICOAGULANT DRUGS IN THE TREATMENT OF PULMONARY EMBOLISM

A CONTROLLED TRIAL

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THE use of an anticoagulant drug in treating venous thrombosis was first reported by Murray et al. (1937) and Crafoord (1937), who administered heparin, and soon there were claims that the number of deaths from pulmonary embolism was thereby reduced.

Bauer (1946) cited 71 cases of pulmonary embolism treated with intravenous heparin with no deaths. Because of the high cost of heparin and the disadvantage of repeated intravenous injections, longer-acting anticoagulant drugs of the coumarin type came into more widespread use. Allen et al. (1947) reported 329 cases of pulmonary embolism treated with heparin and dicoumarol with only 1 death. Bauer (1959) has reported 627 cases of venous thrombosis, treated with heparin alone, with only 5 deaths from pulmonary embolism. Of the 45 other patients who had already had one pulmonary embolism 2 died.

In a retrospective survey covering thirteen years, Barker et al. (1940) found evidence of venous thrombosis or pulmonary embolism in 0·96% of 172,888 postoperative cases untreated with anticoagulants; more than half of their patients with pulmonary embolism died. In other series the mortality in cases of pulmonary embolism has been high: de Takats and Jesser (1940) and Short (1952) reported a mortality of 87% and 23% respectively.

The diagnosis of pulmonary embolism is rarely proved before death. The diagnosis in life rests on a combination of symptoms and signs in the chest and legs and changes in the radiogram and electrocardiogram; and in the less severe cases the diagnosis is more uncertain. For this reason it is unsatisfactory to compare results in series reported by different workers.

There are other objections to this type of comparison. Sudden death is common in pulmonary embolism, and untreated series include patients who died before any effective treatment could have been given. In other cases the diagnosis, unsuspected in life, is made only at necropsy. Cases of these two types will not figure in any treated series.

The risk of hæmorrhage has made many physicians and surgeons unwilling to use anticoagulants routinely in the treatment of pulmonary embolism on existing evidence. There is some further support for scepticism of the protection afforded by anticoagulants in a report by Marks et al. (1954). They reported favourably on the value of anticoagulants in cases of venous thrombosis but found that it did not reduce the incidence of fatal pulmonary emboli. Once pulmonary embolism has occurred it may appear to be too late for anticoagulants to be effective.

Our object has been to measure the effect of anticoagulants in patients who have had one pulmonary embolism, both on the course of the first embolism and on the risk of further attacks. It seemed essential to use the method of observing concurrent series of patients, deciding by chance whether they received anticoagulants or not.

Material and Methods

Selection of Patients

Medical and surgical colleagues were asked to notify us at the first indication that pulmonary embolism might have occurred in any of their patients. Full clinical examination was

carried out without delay and a portable chest radiograph and electrocardiogram were taken. The clinical features on which the diagnosis was based reflected the presence of acute right-sided heart-failure or of pulmonary infarction or both. Right-sided heart-failure usually declared itself with faintness, central chest pain, a fall in blood-pressure, and a rise in jugular venous pressure together with changes in the electrocardiogram. When pulmonary infarction occurred the common findings were pleuritic pain, hæmoptysis, fever, pleural friction, loss of resonance at the lung base, and rales; in these patients it was usual to find changes in the bedside chest radiograph. Tenderness or swelling of the calf or any other signs of thrombophlebitis strengthened the diagnosis, but some of the patients had no abnormal signs in the legs. The clinical features, electrocardiograms, and radiographs of these patients will be fully described in a separate report.

When pulmonary embolism was diagnosed, the suitability of the patient for anticoagulant treatment was considered. The only contraindications to anticoagulants were: (*a*) a recent operation, and (*b*) a history suggestive of recent peptic ulceration. If pulmonary embolism had occurred within a week of an operation the surgeon in charge of the case was asked if anticoagulants could be used. Anticoagulants were seldom withheld except after such operations as mastectomy or prostatectomy where a large raw area had been left. If it was considered that the risk of hæmorrhage was too great the patient was excluded from the series. The fact that a patient was thought to have had more than one episode of pulmonary embolism did not exclude him. The time that elapsed between the first symptom and inclusion in the trial varied from a few minutes to as long as twelve days. It was within twenty-four hours in 41 out of 73 cases.

Envelopes were prepared containing an equal number of cards marked "anticoagulant" or "no anticoagulant", and when a patient was admitted to the trial a card was drawn.

Treatment

All patients were confined to bed for ten days. There were a few whose condition did not allow them to begin to walk on the tenth day. The remainder were encouraged to walk increasing distances and then return to bed; sitting in a chair was forbidden. Where there were signs of venous thrombosis in the leg the foot of the bed was elevated and a cradle used to prevent pressure from bedclothes. Some patients in both groups were given oxygen therapy for severe breathlessness or cyanosis, pressor drugs (L-noradrenaline and mephentermine sulphate) for severe hypotension, and digitalis for atrial fibrillation or paroxysmal tachycardia. Antibiotics were not usually given for pulmonary infarction.

TABLE I—ANTICOAGULANT DOSAGE SCHEME

Actual prothrombin-time (sec.) / Control prothrombin-time (sec.)	Dosage for next 24 hr.*
4–6	1/8 of total dose previous day
4–3	3/4 " " " " "
3–2	Whole " " " " "
2–1 1/2	1 1/4 times " " " "
Under 1 1/2	1 1/2 times " " " "

* Divided into two roughly equal doses, given night and morning.

Those who were to have anticoagulants were treated with heparin and nicoumalone ('Sinthrome'). Heparin was given by intravenous injection 10,000 units every six hours for six doses, without laboratory control. Nicoumalone was begun concurrently and the prothrombin-time estimated by the one-stage Quick test on the third day. Nicoumalone was usually given in the following doses: 16 mg. followed at twelve-hourly intervals by 8, 8, and 4 mg. The dose was then regulated to maintain the prothrombin-time at between two and three times control time. Table I shows the dosage used.

It was never necessary to give an injection of protamine sulphate to counteract the effect of heparin. Vitamin K_1 was administered—probably unnecessarily—to 3 patients who had minor hæmorrhages. Anticoagulants were given for fourteen days except to those who bled and 1 other patient who was thought to have developed drug sensitivity. 5 patients received a longer course of anticoagulants for periods up to twenty-eight days because they were unable to get up from bed on the tenth day.

Findings

The first patient was admitted to the trial in March, 1957. By April, 1958, 35 patients had been included, and at this stage it became necessary to review the further conduct of the trial. Of 19 patients who had not received anticoagulants 5 had died of pulmonary embolism. Of 16 who had received anticoagulants none had died of pulmonary embolism, and 1 had died of suppurative pneumonia with hæmorrhage from a duodenal ulcer as a contributory factor. In addition 5 others in the untreated group had non-fatal recurrences of pulmonary embolism. In the treated group there was no recurrence.

TABLE II—RESULTS IN FIRST 35 CASES

Group	Total	Deaths from pulmonary embolism	Non-fatal recurrences	Other deaths
Untreated ..	19	5	5	0
Treated ..	16	0	0	1

First Stage of Trial (35 cases)

An analysis of the results (table II) showed that the difference in deaths in the two groups from pulmonary embolism was unlikely to be due to chance: P=0·036 (1 in 28). When deaths from pulmonary embolism and non-fatal recurrences were taken together the result was convincing: P=0·0005 (1 in 1987).

In view of this situation it was felt that the trial could not be continued in its original form. The low mortality in the treated series, however, needed confirmation. Accordingly the trial was continued with the same criteria for inclusion, but thereafter all patients were to receive anticoagulant treatment. By July, 1959, a total of 54 patients had been treated with anticoagulants and the trial was stopped.

Complete Series (73 cases)

To test the significance of the results (table III) the following comparisons were made:

Deaths from pulmonary embolism.—Untreated cases 5 out of 19, treated cases 0 out of 54: P=0·0007 or 1 in 1292.

Deaths from pulmonary embolism added to non-fatal recurrences.—Untreated cases 10 out of 19, treated cases 1 out of 54: P=0·0000014 or 1 in 704,225.

Deaths from all causes.—Untreated group 5 out of 19, treated group 2 out of 54: P=0·011 or 1 in 90.

Deaths

The 5 deaths in the untreated group were all due to pulmonary embolism.

Case 1.—A woman of 56 with carcinoma of the breast and pelvic metastases. Massive pulmonary embolism occurred four days after admission to hospital and was followed by steadily increasing signs of infarction of both lungs. The patient became increasingly dyspnœic and produced terminally large quantities of very offensive sputum. She died twenty-one days after the first symptom of embolism, and necropsy showed massive pulmonary infarction with cavitation. There were large, organising clots in both main pulmonary arteries but no very recent thrombi.

TABLE III—RESULTS IN COMPLETE SERIES OF 73 CASES

Group	Total	Deaths from pulmonary embolism	Non-fatal recurrences	Other deaths
Untreated ..	19	5	5	0
Treated ..	54	0	1	2

Case 2.—A man of 56 who five days after a second laparotomy for intestinal obstruction developed very severe constricting central chest pain and signs of right-sided heart-failure. The presence of extensive thrombophlebitis of the leg and the recurrence of slight hæmoptysis pointed to the diagnosis. He survived for forty-eight hours after massive pulmonary embolism. In addition to the thrombophlebitis of the leg, large clots were found in the hepatic veins that were thought to be the result of pylephlebitis.

Case 3.—A 78-year-old woman had severe pulmonary embolism twenty-one days after an operation to reduce a Pott's fracture. She died suddenly twelve days later, and necropsy revealed large fresh clots in the main pulmonary artery.

Case 4.—A man of 57 who had had a cerebral thrombosis six years previously developed thrombophlebitis of the right leg. Right pleural pain and hæmoptysis led to the diagnosis of pulmonary embolism, and he was admitted to the trial. One day later sudden breathlessness, severe hypotension, and obvious electrocardiographic changes gave evidence of a second large embolism. He developed increasing signs of bilateral pulmonary infarction with fœtid sputum and swinging fever. He survived for fifteen days after the second episode. At necropsy there were large clots in both pulmonary arteries and massive infarction of the lower lobes of both lungs with cavitation.

Case 5.—A 41-year-old man survived for fourteen days after the first symptoms of pulmonary embolism. He had been admitted to hospital for treatment of the nephrotic syndrome. Six days before his death signs of acute pulmonary œdema developed, but he recovered from this attack and improved after treatment with diuretics. He died during a major epileptic fit. Necropsy showed that his renal disease was due to primary amyloidosis. Large clots were found in the pulmonary arteries, and in the left lower lobe the pulmonary vein was filled with clot which was continuous with a mass of clot 6 cm. × $3^1/_2$ cm. × $3^1/_2$ cm. lying in the left atrium. Emboli were found saddling the bifurcation of both common carotid arteries. Pulmonary œdema had presumably been caused by the obstruction in the left atrium, and the immediate cause of death was cerebral infarction.

Of the 2 deaths in the treated series which are now to be described, the 1st was due to suppurative pneumonia complicated by hæmorrhage from a duodenal ulcer; and the 2nd was due to anuria resulting from necrosis of the renal tubules of unknown cause.

Case 6.—A woman of 68 years, known to have hypertension, was admitted to a mental hospital with a diagnosis of depression. Intestinal obstruction was found, and she was transferred to this hospital where a strangulated hernia was repaired. After operation she ran a very low-grade fever and on one occasion auricular fibrillation was thought to have developed. An electrocardiogram on the same day showed sinus rhythm. Six days after operation she complained of severe right pleural pain of sudden onset. Friction was to be heard; and there were dullness to percussion, and rales at the right base. She coughed blood-stained sputum which increased in amount. A portable chest X-ray showed extensive shadowing at the right base and mid-zone. Electrocardiography revealed hypertensive changes only.

No adequate history could be obtained from the patient. She was admitted to the trial, and after a card had been drawn anticoagulants were begun. Supervision of the dosage of nicoumalone was inadequate, and on the fourth day of treatment her prothrombin-time was prolonged to eight times normal. Again on the sixth day it was between five and six times normal.

Her condition deteriorated and greater quantities of purulent sputum were produced. On the ninth day of treatment melæna was noticed and anticoagulants were stopped. She died on the following day. Necropsy revealed suppurative pneumonia with abscess formation which was presumed to have followed inhalation of vomit. There was also a subacute duodenal ulcer in the base of which a small artery had been eroded. Considerable intestinal hæmorrhage had occurred. Minor pulmonary emboli were found, and there were antemortem thrombi in the calves of both legs and in the right long saphenous vein. Suppurative pneumonia was considered to be the major cause of death, but intestinal bleeding was an important contributory factor, and this death has therefore been classified as due to treatment.

Case 7.—A man of 52 developed superficial thrombophlebitis of the left leg for which he was given phenylbutazone. This was discontinued when an erythematous rash developed. Three weeks later superficial thrombophlebitis appeared in the right leg, followed in a further two weeks by pulmonary embolism. He was later admitted to hospital where superficial thrombophlebitis of the left long saphenous vein, tenderness of both calves, and bilateral pulmonary infarction were found. During eighteen days' treatment with phenindione the signs of pulmonary infarction and of phlebitis subsided and he was discharged home. Two weeks later he was readmitted with pleural pain and was found to have pain and swelling again in both calves and signs of bilateral pulmonary infarction. There was no fall in blood-pressure. He was admitted to the trial and treatment was begun with heparin and phenindione. That phenindione rather than nicoumalone had mistakenly been prescribed was not realised for several days, and it was then thought that the treatment should continue unchanged. In addition to phenindione, butobarbitone was also given at night. On the twelfth day of treatment a generalised erythematous rash appeared, followed by fever and diarrhœa. All drugs were withheld. Oliguria and later anuria developed, and the blood-urea rose to 560 mg. per 100 ml. He died suddenly four weeks after the appearance of the skin rash which followed the second course of phenindione. Necropsy confirmed the diagnosis of thrombophlebitis of both legs and old pulmonary infarction. Death was due to extensive renal tubular necrosis and uræmia.

The cause of the renal lesion is unknown. There was no period of hypotension. It was felt that the skin eruption could have been due to sensitivity to the phenindione or butobarbitone which he was taking.

Recurrences

In the first stage of the trial there were during the trial period (i.e., fourteen days) 5 non-fatal recurrences of embolism in the untreated group and no recurrences in the treated group. Among the 54 treated patients in the complete series there was 1 non-fatal recurrence.

Subsequent Progress

After the trial period it was not possible to keep all the patients under review. The fate of the 29 survivors of the first period of the trial is known. In 1 of the untreated group a further embolism developed eight weeks after the trial period, following a second operation on her fractured neck of femur. This was the only recurrence in a follow-up ranging from twelve to twenty-four months. 2 of the patients in the later series were readmitted to hospital with recurrence of infarction in the fourth week after completing the fourteen-day course of anticoagulant treatment.

Effect of Anticoagulants on Leg Vein Thrombosis

No attempt was made to assess the progress of the venous lesions of the legs in all patients with tenderness or swelling. In 3 patients who were being treated with anticoagulants there was obvious extension of superficial thrombophlebitis.

Severity of Cases in the Two Groups

Evidence of stress on the right side of the heart indicates that the embolism is massive (Wood 1950). In all the cases records were kept of the presence or absence of a significant fall of blood-pressure and of severe electrocardiographic changes, and these were the two criteria we have used in defining which cases were " severe " and which were not. The changes which were sought in the electrocardiogram were those described by Cutforth and Oram (1958), inversion of the T waves in leads II, AVF and V_2, and the

presence of right bundle-branch block. Using these criteria there were 20 severe cases. All had a considerable fall in blood-pressure, 15 fulfilled both criteria; and in 1 other the electrocardiographic evidence of severity was dubious. The distribution of the severe cases was similar in the two groups.

Severe cases.—Untreated cases 6 out of 19, treated cases 14 out of 54: χ^2 (with Yates' correction) $= 0{\cdot}031$ $0{\cdot}8 < P < 0{\cdot}9$.

Lung Changes with Stress on Right Side of Heart

Of the 20 patients with evidence of stress on the right side of the heart, some later had massive pulmonary infarction while others showed neither clinical nor X-ray evidence of this. Lung changes were more in evidence in the 6 severe cases from the untreated group. Of these 6, 2 died (cases 1 and 4) of massive pulmonary infarction with virtual dissolution of the lower zones of both lungs. Nothing like this was seen in any of the treated cases. Of the remaining 4 severe cases in the untreated group, 1 died within forty-eight hours and 2 of the other 3 had extensive pulmonary infarction but recovered. Of the 14 severe cases in the treated group, 2 recovered without clinical signs or X-ray evidence of infarction and in 2 others only a few rales and no radiographic changes developed. Thus anticoagulants appeared to diminish the extent of pulmonary infarction.

Mistaken Diagnoses

The diagnosis was proved wrong in case 6 (already described) and in 1 other patient who came to necropsy. Again suppurative pneumonia following œsophageal rupture after instrumentation was found. No anticoagulants had been given, and this patient does not therefore figure in the final analysis of the results.

Discussion

The first conclusion drawn from this trial is that in a patient who has already had pulmonary embolism the subsequent course of the disease is affected by the regime of anticoagulant therapy we have used: the mortality of pulmonary embolism is reduced. The results show that deaths from pulmonary embolism are likely to outnumber the deaths that may be attributed to treatment.

In the *treated group* we have assumed that the 1 fatal case of renal tubular necrosis was caused by the anticoagulant drug. In the other fatal treated case other factors were important in causing death.

Of the 5 deaths in the *untreated group* only 1 followed immediately the lodging of a second embolism in the pulmonary artery (case 3). In 1 other a second embolism occurred the day after his inclusion in the trial, but the patient lived a further fifteen days (case 4). In the others, only one episode of embolism was diagnosed and the three patients lived for two, fourteen, and twenty-one days. 2 of the 5 deaths were due to very extensive pulmonary infarction with superadded infection and cavitation. In another, death was due to extension of the thrombus through the pulmonary veins to fill the left atrium. These 5 cases suggest that the idea that it is too late to use anticoagulant treatment when a pulmonary embolism has already occurred is ill founded.

There were no comparable deaths in the treated group, even in the most severe cases; and it seems reasonable therefore to conclude that even after embolism has reached the pulmonary arteries anticoagulant therapy reduces the risk of death from heart-failure or from pulmonary infarction—probably by discouraging further deposition of thrombus in the pulmonary arteries where the blood-flow is so grossly impeded. This would explain its effect in diminishing the extent of subsequent pulmonary infarction.

2 patients died very quickly after the first signs of embolism. We have, however, been impressed by the fact that every patient in this series who received the first injection of heparin survived. This suggests that there is no longer any place for considering Trendelenburg's operation of pulmonary embolectomy. One of our patients required long-continued infusions of L-noradrenaline, and several others required repeated intravenous injections of mephentermine sulphate to maintain the blood-pressure. All subsequently recovered. No instance of chronic cor pulmonale has yet been diagnosed in these cases.

The diagnosis of pulmonary embolism can never be established with absolute certainty during life, and there is always a risk of mistakenly treating postoperative pneumonia with anticoagulants. This not only entails additional risk, but also deprives the patient of the benefit of specific treatment. Case 6 shows that the two conditions may arise in one patient at the same time.

Without close supervision of the administration of the anticoagulant, unnecessary deaths may occur, as in case 6, who had extensive intestinal hæmorrhage at a time when the prothrombin-time was unduly prolonged.

Summary

73 patients in whom pulmonary embolism had been diagnosed and in whom there was no contraindication to anticoagulant therapy were admitted to a clinical trial. One group were to receive treatment without anticoagulants, and the other heparin and nicoumalone (' Sinthrome '). The treatment period was fourteen days.

In the first 35 patients a card was drawn to decide whether anticoagulants should be used or not. Of the 19 untreated cases 5 died and 5 others had non-fatal recurrences of embolism. Of the 16 cases treated with anticoagulants 1 died and none had recurrences of embolism. The 1 death in the treated series was due to a combination of suppurative pneumonia and alimentary bleeding.

No further cases were admitted to the untreated series, but 38 others were taken into the treated group, making a total of 54. There was only 1 further death, and this was due to renal tubular necrosis in a patient mistakenly treated with phenindione instead of nicoumalone.

It is concluded that when a patient has had pulmonary embolism, heparin and nicoumalone reduce the risk of death from that embolism. The likelihood of recurrent embolism is also diminished.

Prof. C. Bruce Perry, Dr. J. E. Cates, Dr. D. H. Davies, Dr. J. E. G. Pearson, and Dr. J. A. Cosh suggested the form of this trial and the type of treatment that should be tested. We are indebted to them, and to all the physicians and surgeons of the United Bristol Hospitals who allowed us to include their patients.

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Addendum

Since this paper was completed R. H. Brooks and H. B. Calleja (*Ann. intern. Med.* 1960, **52**, 706) have reported the occurrence of a nephropathy accompanying a generalised sensitivity reaction to phenylindione. Their patient developed fever, hepatitis, and a rash; and the urine contained albumin, casts, and red blood-cells. Recovery was complete.

A PITUITARY-DEPENDENT INHIBITOR OF GLUCOSE UPTAKE BY MUSCLE IN PROTEIN FRACTIONS OF HUMAN PLASMA

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WHEN protein fractions are prepared from normal human serum by zone electrophoresis on columns of treated cellulose, insulin may be detected in fractions containing α_1-globulins, β-globulins, and γ-globulins by their stimulating effect on the uptake of glucose by isolated rat diaphragm (Randle and Taylor 1958, Taylor and Randle 1959). During these experiments we noted that whereas some α_2-globulin fractions stimulate uptake of glucose, others depress it or are without effect. Since the α_2-globulins migrate on electrophoresis between fractions containing substantial amounts of insulin (albumin+α_1-globulin and β-globulin fractions), it seemed possible for an inhibitor of glucose uptake to be present in α_2-globulin fractions, but for its activity to be masked in some samples by insulin derived from adjacent fractions. This expectation has now been realised in experiments in which α_2-globulins were more effectively separated from normal human plasma by a combination of fractional precipitation with ethanol and zone electrophoresis. Since α_2-globulins prepared from plasma in this way have consistently inhibited the uptake of glucose by diaphragm, it seemed important to test similar protein fractions prepared from the plasma of hypophysectomised patients and from patients with panhypopituitarism both before and after treatment with human growth hormone (H.G.H.). We here present the results of these experiments.

Methods and Procedure

Blood Samples

Blood was collected from an antecubital vein with a clean dry syringe and diluted immediately with acid-citrate-dextrose (A.C.D.) 0·173 volumes (Lever et al. 1951). The A.C.D.-plasma was then separated by centrifugation.

Patients

Blood samples were collected from hypophysectomised patients or from patients with panhypopituitarism who were maintained on cortisone and thyroxine. Blood samples from diabetic hypophysectomised patients were collected about 24 hours after the last injection of insulin zinc suspension ('Lente'). When H.G.H. was given (5 or 10 mg. by subcutaneous injection) blood was collected 18–24 hours after injection of the hormone. The H.G.H. used in these studies was prepared from human pituitaries by methods already described (Taylor and Randle 1959).

Preparation of Protein Fractions

The proteins of A.C.D.-plasma were separated into three fractions by fractional precipitation with cold ethanol after the method of Lever et al. (1951). The fractions were dialysed at room temperature against distilled water, and then freeze-dried. They are designated according to Lever et al. at I+III (mainly α_2 and β globulins and fibrinogen); II (γ-globulins); and IV, V, and VI (mainly albumin and α-globulins, with some β-globulins). The composition of these fractions was confirmed by paper electrophoresis using the technique of Flynn and de Mayo (1951) and the protein-staining method of Henry et al. (1957).

Subfractionation of IV, V, and VI.—Fraction IV, V, and VI, prepared as above, was subfractionated by zone electrophoresis on columns of treated cellulose, using an improved method (Naughton and Taylor 1960). Three subfractions were separated (albumin+α_1-globulins, α_2-globulins, and β-globulins), dialysed at room temperature against distilled water, and freeze-dried.

Assay of Biological Activity

The effect of each protein fraction or subfraction on the uptake of glucose by isolated rat diaphragm was tested as described previously (Randle and Taylor 1958). Insulin was deemed to be present if a fraction or subfraction enhanced glucose uptake significantly (Taylor and Randle 1959), and an inhibitor was deemed to be present if glucose uptake was diminished significantly. Each fraction or subfraction was dissolved in bicarbonate-buffered salt-solution (Gey and Gey 1936) of three times the volume of the plasma from which the fraction was prepared (for assay of biological activity). Fraction I+III (containing fibrinogen) clotted at this stage; the clot was allowed to form and was then removed by centrifugation.

Results

The effects of protein fractions of normal human plasma on the uptake of glucose by diaphragm are shown in tables I and II. Fraction II (γ-globulins) had no demonstrable effect on glucose uptake. Fraction I+III (mainly α_2 and β globulins) consistently stimulated glucose uptake. The effect of fraction IV, V, and VI (mainly albumin and α_2-globulins, with some β-globulins) was not consistent; whereas many samples inhibited the uptake of glucose significantly, others had no significant effect. When fraction IV, V, and VI was subfractionated by zone electrophoresis, however, the albumin/α_1-globulin subfraction enhanced glucose uptake, whereas the α_2 and β globulin subfractions inhibited glucose uptake. Moreover, the sum of the effects of individual subfractions was very similar to that of the fraction from which they were prepared.

TABLE I—EFFECT OF PROTEIN FRACTIONS OF NORMAL HUMAN PLASMA ON UPTAKE OF GLUCOSE BY DIAPHRAGM

Glucose uptake (difference from control incubated in buffer alone): mean difference ± S.E. of difference (mg. glucose per. g. wet diaphragm per hr.):

Fraction I+III	Fraction II	Fraction IV, V and VI
1·3±0·25§	0·3±0·3‡	−0·6±0·25‖

For differences marked ‡ $P<0.001$; § $P<0.01>0.001$; ‖ $P<0.05>0.01$; and for other differences $P>0.05$.

Each difference is derived from means of 36 observations (fractions I+III and II) or 54 observations (fractions IV, V and VI). 6 plasma samples were tested from fractions I+III and II, and 9 plasma samples from fractions IV, V and VI.

The effects of protein fractions from the plasma of hypophysectomised patients were noticeably different from those of comparable fractions of normal human plasma. Thus glucose uptake was increased by fraction IV, V, and VI, and by the α_2 and β globulin subfractions thereof, whereas comparable fractions from normal human plasma inhibited glucose uptake. The differences were less with protein fractions of plasma from patients with panhypopituitarism, and some inhibition was seen with the β-globulin subfraction of fraction IV, V, and VI (table II). The effect of hypophysectomy on the inhibitory activity of α_2-globulin and β-globulin subfractions is shown by the results of experiments with plasma from an acromegalic patient before and after hypophysectomy (table III).

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TABLE II—EFFECT ON GLUCOSE UPTAKE OF DIAPHRAGM OF PROTEIN FRACTIONS FROM NORMAL PLASMA AND PLASMA FROM HYPOPHYSECTOMISED PATIENTS, OR PATIENTS WITH PANHYPOPITUITARISM

Source of serum and protein fractions	Case no.	Glucose uptake (difference from control incubated in buffer alone): mean difference ± S.E. of difference (mg. glucose per g. wet diaphragm per hr.)			
		Fraction IV, V, and VI	Subfractions of IV, V, and VI		
			Albumin + α_1-globulin	α_2-globulin	β-globulin
Normal plasma	1–9 (pooled results)	−0·6 ± 0·25	..	..	..
	7	−0·5 ± 0·29	0·1 ± 0·62	−0·6 ± 0·70	0·1 ± 0·62
	8	−0·4 ± 0·75	1·9 ± 0·48§	−1·5 ± 0·39§	−1·2 ± 0·35‖
	9	−0·3 ± 0·31	1·5 ± 0·32‡	−0·6 ± 0·39	−1·1 ± 0·34§
	Pooled	..	1·2 ± 0·29‡	−0·9 ± 0·28§	−0·8 ± 0·25§
Hypophysectomised patients	1	0·6 ± 0·39	..	..	..
	2	0·1 ± 0·36	..	..	..
	3	0·7 ± 0·50	..	..	..
	4	..	1·8 ± 0·47§	0·4 ± 0·34	1·9 ± 0·36‡
	5	..	2·2 ± 0·42‡	1·9 ± 0·49§	0·6 ± 0·25‖
	Pooled	0·5 ± 0·28	2·0 ± 0·3‡	1·2 ± 0·28§	1·3 ± 0·21‡
Panhypopituitarism	1	0·0 ± 0·60	1·1 ± 0·67	−0·1 ± 0·49	−0·8 ± 0·56
	2	0·2 ± 0·84	0·4 ± 0·37	0·1 ± 0·32	−0·2 ± 0·37
	Pooled	0·1 ± 0·5	0·8 ± 0·37	0·0 ± 0·27	−0·5 ± 0·31

For differences marked ‡ $P<0·001$; § $P<0·01>0·05$; ‖ $P<0·05>0·01$; and for other differences $P>0·05$.
Each difference is derived from means of 6 observations. Hypophysectomised patients 2, 3, and 5 were also diabetic.

The effects of H.G.H. on the biological activity of protein fractions of plasma from patients with panhypopituitarism are shown in table IV. Before treatment with H.G.H. none of the protein fractions showed significant inhibitory activity; after treatment significant inhibition was noted with both α_2 and β globulin subfractions. This effect of H.G.H. was greatest with α_2-globulin subfractions.

Discussion

We conclude from the results of our investigations that insulin is present in the albumin/α_1-globulin and β-globulin fractions of normal human plasma, and that an inhibitor of glucose uptake is present in the α_2 and β globulin fractions. The presence of this inhibitor in protein fractions of human plasma seems to depend upon whether pituitary growth hormone is available. Neither insulin nor inhibitor could be detected in γ-globulins.

When zone electrophoresis was previously used alone, insulin was detected in the albumin/α_1-globulin, β-globulin, and γ-globulin fractions, and an inhibitor was occasionally found in the α_2-globulin fractions (Randle and Taylor 1958). In these studies insulin in the γ-globulins may have resulted from contamination with β-globulins containing the hormone, and failure to obtain consistent inhibition with α_2-globulins may have been due to contamination of α_2-globulins with insulin from adjacent fractions. These views were justified by the present investigation, where a more refined method of plasma-protein fractionation yielded γ-globulin fractions which seem to be free of insulin, and α_2-globulin fractions which consistently inhibit the uptake of glucose by diaphragm.

The inhibitor identified in these studies is interesting in relation to growth hormone and its diabetogenic effect in man.

TABLE III—EFFECT OF HYPOPHYSECTOMY ON BIOLOGICAL ACTIVITY OF PROTEIN FRACTIONS OF HUMAN PLASMA

Subfraction of IV, V, and VI	Glucose uptake (difference from control incubated in buffer alone): mean difference ± S.E. of difference (mg. glucose per g. wet diaphragm per hr.)		
	Before hypophysectomy	After hypophysectomy	Difference
Albumin + α_1-globulin	0·0 ± 0·42	1·8 ± 0·47§	1·8 ± p·63‖
α_2-globulin	−0·8 ± 0·42	0·4 ± 0·34	1·2 ± 0·52‖
β-globulin	−0·4 ± 0·45	1·9 ± 0·36‡	2·3 ± 0·58§

For differences marked ‡ $P<0·001$; § $P<0·05>0·001$; and for other differences $P>0·05$.
Plasma samples were taken before and after hypophysectomy from an acromegalic patient. Each difference is derived from means of 6 observations.

Experiments have shown that, when rats are treated with ox growth hormone, the in-vitro uptake of glucose by isolated diaphragm and the sensitivity to insulin are reduced (Manchester, Randle, and Young 1959); whereas, when ox growth hormone is added in vitro, glucose uptake is not inhibited and sensitivity to insulin is not reduced. This has led to the view that growth hormone is coverted in vivo to a substance with these properties, or alternatively that another substance is released in vivo under the influence of growth hormone. Experimental evidence has accrued from the studies of Bornstein and Park

TABLE IV—EFFECT OF TREATMENT WITH HUMAN GROWTH HORMONE ON THE BIOLOGICAL ACTIVITY OF PROTEIN FRACTIONS FROM HYPOPHYSECTOMISED PATIENTS OR PATIENTS WITH PANHYPOPITUITARISM

Fraction	Subfraction of IV, V, and VI	Glucose uptake (difference from control incubated in buffer alone): mean difference ± S.E. of difference (mg. glucose per g. wet diaphragm per hr.)		
		Before H.G.H.	After H.G.H.	Effect of H.G.H.
IV, V, and VI	..	0·3 ± 0·3	−0·4 ± 0·18	−0·7 ± 0·35
	Albumin + α_1-globulin	0·9 ± 0·37‖	0·3 ± 0·29	−0·6 ± 0·47
	α_2-globulin	0 ± 0·29	−1·0 ± 0·28§	−1·0 ± 0·40‖
	β-globulin	−0·5 ± 0·32	−0·9 ± 0·27§	−0·4 ± 0·42

For differences marked § $P<0·01>0·001$; ‖ $P<0·05>0·01$; and for other differences $P>0·05$.
For fraction IV, V, and VI the pooled results from one hypophysectomised patient and three patients with panhypopituitarism are given (each difference being derived from means of 18 observations).
For subfractions the pooled results from three patients with panhypopituitarism are given (each difference being derived from means of 12 observations).

(1953), Bornstein (1953), Whitney and Young (1957), Vallance-Owen and Lukens (1957), and Krahl et al. (1959). These workers have identified in the plasma of rats or cats a factor which inhibits the effects of insulin (or of serum-albumin which contains insulin) on the uptake of glucose by diaphragm, the presence of which is conditioned by the availability of growth hormone and cortisol (or its analogues).

Our findings in man are in keeping with these observations in animals; for, whereas H.G.H. does not inhibit the uptake of glucose by diaphragm (table V), it does seem to provoke an inhibitor in plasma when injected into patients. We do not know whether cortisol is also necessary for the formation of the inhibitor which we have identified in human plasma. Whether this inhibitor is formed from growth hormone or released under its influence cannot be decided at present.

Vallance-Owen et al. (1958) have previously identified in albumin fractions of human plasma a factor which is capable of antagonising the effects of insulin on glucose uptake and which is pituitary dependent. Our factor

seems to be different in that it is associated with α_2 and β globulin fractions; it inhibits the uptake of glucose in the absence of added insulin, and it is not lost during zone electrophoresis on columns of treated cellulose (cf. Vallance-Owen et al. 1958). A factor which inhibits the uptake of glucose by diaphragm without added insulin has been identified in the residues of an acid/alcohol extract of human plasma by Baird and Bornstein (1957). We do not know whether this factor is similar to the one detected in our investigation. The physiological and pathological significance of this inhibitor of glucose uptake will only be appreciated when its exact relation to growth hormone, and to the ætiology of diabetes and its complications, has been defined.

TABLE V—EFFECT OF HUMAN GROWTH HORMONE ON UPTAKE OF GLUCOSE BY ISOLATED RAT DIAPHRAGM

Concentration of H.G.H. (μg. per ml.)	Glucose uptake: mean ± S.E. (mg. glucose per g. wet diaphragm per hr.)
None	4·1 ± 0·35 (6)
11·5	4·2 ± 0·20 (6)
2·3	3·9 ± 0·23 (6)
0·46	4·3 ± 0·40 (6)

The number of observations is given in parentheses.

Our studies have also shown that a protein fraction of human plasma (fraction IV, V, and VI) which inhibits the uptake of glucose by diaphragm may be resolved by further subfractionation into a fraction with demonstrable insulin activity (i.e., which stimulates glucose uptake) and fractions containing an inhibitor of glucose uptake. This illustrates strikingly how misleading plasma-insulin assays may be when they are based on the effects of untreated plasma on the uptake of glucose by isolated rat diaphragm (cf. Randle 1954).

Summary

Protein fractions were prepared from human plasma by a combination of fractional precipitation with ethanol and zone electrophoresis on columns of treated cellulose, and their effect on the uptake of glucose by isolated rat diaphragm in vitro was investigated.

Insulin was detected in fractions containing albumin and α_1-globulins, and β-globulins. An inhibitor of glucose uptake by diaphragm was detected in α_2 and β globulin fractions of normal human plasma, though not in the corresponding protein fractions of plasma from hypophysectomised patients or patients with panhypopituitarism.

Treatment of hypophysectomised or panhypopituitary patients with human growth hormone led to the reappearance of inhibitor activity in α_2 and β globulin fractions.

Since growth hormone itself does not inhibit the uptake of glucose by diaphragm, either growth hormone is converted to an inhibitor in vivo or it promotes the release of an inhibitor.

We wish to thank Prof. F. G. Young for his interest and encouragement. We are greatly indebted to Dr. L. C. Martin of Addenbrooke's Hospital, Cambridge, to Dr. R. Luft of the Department of Endocrinology, Serafimerlasarettet, Stockholm, to Dr. T. M. Chalmers of the Middlesex Hospital, and to Prof. F. T. G. Prunty of St. Thomas's Hospital, for samples of blood from hypophysectomised or panhypopituitary patients; to several colleagues for samples of normal human plasma; and to Mrs. W. Thorne for skilled technical assistance. The cost of these investigations was defrayed in part by grants for research expenses (to K. W. T.) from the British Diabetic Association and the Elmore Research Fund, University of Cambridge, and (to P. J. R.) fr m the Medical Research Council.

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THE EFFECT OF INTRAGASTRIC OXYGEN ON THE OXYGENATION OF ARTERIAL AND PORTAL BLOOD IN HYPOXIC ANIMALS

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IN 1950 Åkerrén and Fürstenburg claimed favourable effects from the administration of oxygen by gastric tube to anoxic infants, and their work attracted attention in Great Britain although this form of treatment had been advocated earlier by Ylppö (1935). Later Waller and Morris (1953) reported good results using Åkerrén and Fürstenberg's technique, and the method has remained popular (e.g., Leys 1957). Although Åkerrén and Fürstenberg quoted data from other sources in support of their procedure, neither they nor the later workers cited above have provided clear quantitative evidence by which to assess its efficacy. Moreover full account has not been taken of factors incidental to rather than peculiar to resuscitation by intragastric oxygen in its evaluation.

In 1954, when the possible dangers of overdosage of infants with oxygen were becoming recognised, some work in this laboratory (Banister, Kay, and Coxon 1954) was aimed at developing a means of monitoring oxygen therapy for infants, and in a few experiments (Dr. Philip Banister, unpublished) the effects of intragastric oxygen were studied in young kittens. Since then various opportunities have arisen for measuring the oxygen saturation in samples of arterial or portal blood of cats and puppies before and after gastric insufflation. These experiments were usually designed with some other objective, such as the calibration of oximetric cuvettes (see Kay and Coxon 1957), but for present purposes data have been selected from experiments where other manœuvres were not likely to interfere with the interpretation of the blood-saturation figures.

Methods and Materials

Twenty adult cats (males and females), weighing between 2·3 and 4·0 kg., two kittens each weighing 0·75 kg., and two litter-mate male puppies each weighing 4·4 kg. were used. The animals were anæsthetised with pentobarbitone sodium injected intraperitoneally in a dosage of 40 mg. per kg. body-weight.

Anoxæmia was generally induced by injecting 0·9% sodium-chloride solution at body temperature into one or both pleural cavities to collapse the underlying lung; occasionally depression of respiration by the anæsthetic sufficed. Samples of blood were obtained via a metal cannula inserted into the femoral artery, or through a polyethylene catheter inserted at laparotomy through the splenic vein into the portal vein. The tip

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of the portal catheter was sited headward of the point of entry of the vessels draining the lesser curve of the stomach, and its position was checked by palpation during life and by inspection post mortem.

Oxygen was given via a humidifier and warmer, at 0·5–1·0 litre per minute and 100 mm. water pressure, through a plastic tube of 4 mm. internal diameter which entered the stomach via the mouth. In most animals a similar exit tube was also provided, leading into a bubbler which signalled continuity of flow. The tips of both entry and exit tubes lay within the body of the stomach.

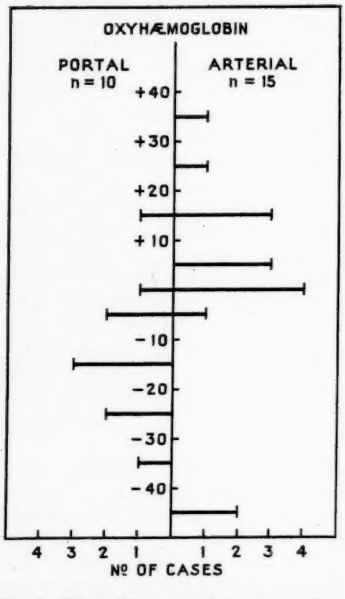

Fig. 1—Effect of intragastric oxygen on the hæmoglobin saturation in arterial and portal blood of hypoxic cats.

The values on the vertical scale indicate changes in percentage saturation, while the length of the horizontal bars corresponds to the number of cases in which the given change was observed.

Observations on arterial blood are plotted to the right of the central axis and observations on portal blood to the left: n=total number of cases studied.

Blood samples were stored in gas-tight syringes at 0°C before analysis for oxygen content and capacity by the manometric method of Van Slyke and Neil (1924).

Results

The results for arterial blood, summarised in fig. 1, seem at first sight to indicate some rise in hæmoglobin saturation after treatment with gastric oxygen. On the other hand, the results for portal blood (also shown in fig. 1) reveal in most cases (eight out of ten) a deterioration in oxygenation after treatment. But the arterial figures assume a rather different significance when compared, as in fig. 2, with the findings when no treatment was given or when air was used instead of oxygen.

These experiments suggest that extra oxygen conferred no definite benefit on the animals exposed to it. In interpreting figs. 1 and 2 it must be noted that the improvement in oxygenation was never limited by full saturation being reached. Blood samples were taken at various intervals from 2 to 20 minutes (mean interval 10 minutes) after insufflation was started, but no correlation was found between the duration of treatment with oxygen and improvement in hæmoglobin saturation. Of the two kittens studied one showed a considerable fall (28%) and the other a slight rise (12%) in portal oxygenation after treatment.

One clear set of data from a puppy are presented in fig. 3. This animal was hypoxic as a result of deep anæsthesia with respiratory depression. Intragastric oxygen was ineffective in this case, although a very high degree of arterial saturation was maintained by intratracheal oxygen. The arterial oxygenation of the other puppy fell slightly (8%) after intragastric oxygen.

Discussion

When Åkerrén and Fürstenberg (1950) described the favourable effect of intragastric oxygen in the resuscitation of asphyxiated infants they put forward as a possible explanation a calculation of what amounts to the "diffusing capacity" for oxygen of the infantile gastrointestinal tract. Their estimate was based ultimately upon measurements made in two cats by McIver et al. (1926), and the justification for including intestinal mucosa in the calculation of the rate of gas absorption after intragastric administration was the radiographic demonstration by Åkerrén et al. of extensive gas bubbles in a baby's jejunal and ileal loops. Similarly, in the present series of animal experiments, there was frequent abdominal distension (confirmed as being intestinal by direct inspection at laparotomy), and many of the animals passed much flatus during gastric insufflation, even though their oral outflow was completely free. Using the data of McIver et al., and making some favourable assumptions, Åkerrén and Fürstenberg concluded that oxygen could be transferred across the gut to the portal blood in large enough amounts and rapidly enough to make a significant contribution to the metabolic needs of a hypoxic infant.

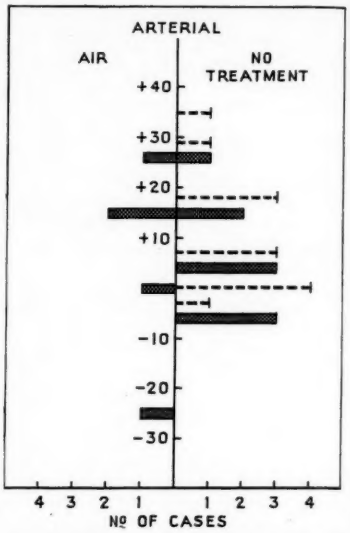

Fig. 2—Effect of intragastric air and of simple passage of time ("no treatment") on the arterial hæmoglobin saturation of hypoxic cats.

The solid bars indicate the number of cases in which the saturation corresponds to that shown on the vertical scale. The interrupted bars reproduce some arterial data from fig. 1 for comparison.

The average time-lapse in the no-treatment cases was 15 minutes and in the air-treated cases 11 minutes.

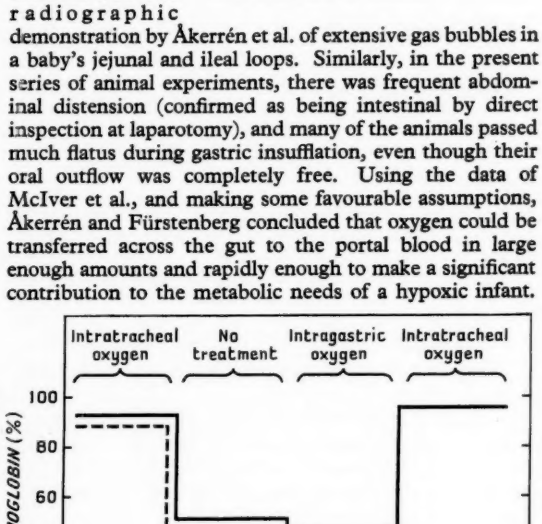

Fig. 3—Time course of changes in arterial and portal oxygen saturation in a puppy undergoing various forms of treatment.

The solid line represents arterial oxyhæmoglobin as a percentage of the total hæmoglobin, and the interrupted line represents the corresponding values for portal blood.

But, although the calculations represented a laudable effort to provide a theoretical basis for Åkerrén and Fürstenberg's therapeutic claims, direct evidence of improved portal or arterial oxygenation was not obtained. Later advocates of intragastric oxygen have assessed their results almost exclusively in descriptive rather than quantitative terms. One of the few reports traced where actual measurements of hæmoglobin saturation were made was that of the findings of James et al. (1959) in a prematurely delivered human fœtus weighing 400 g. Here the substitution of intragastric for intrathecal oxygen caused an abrupt fall in aortic saturation, which was rapidly counteracted when intratracheal oxygen was resumed. The events in this case thus resembled closely those in the puppy represented in fig. 3.

Fig. 2 shows clearly that, among the anoxic cats in the present series, those which were given intragastric oxygen did not, as a group, display any consistent advantage over the control animals which were not treated or which had insufflation of room air. It might be argued that, when improvement appeared to follow intragastric insufflation, this was attributable to reflex stimulation of respiratory movements by the œsophageal tubes, or possibly by stretching of the stomach and adjacent structures, coupled with a high concentration of oxygen in the pharynx from leakage round the tubes. Stimulation of respiratory movements by traction on the upper abdominal viscera is recognised (Guedel 1936, Reeve et al. 1951), and, in the laboratory, sustained pressure on the lower sternal region will often promote rhythmical excursions of the chest wall in deeply anæsthetised animals. Such factors might well come into play when the stomach is distended with gas, and, if in fact such reflex effects are concerned, intragastric oxygen should be more beneficial in anoxia which is due to depressed activity of the respiratory centre than in that due to pulmonary abnormalities.

Some at least of the clinical reports (e.g., Waller and Morris 1953) state that cyanosis was seen to disappear after intragastric oxygen was given but before breathing had started. This sequence of events is clearly incompatible with the idea that mechanical stimulation of respiratory movement is the primary effect of intragastric oxygen. The remarkable resistance of newborn animals to hypoxia may be relevant in this connection; a puppy on the first day of life may withstand about 40 minutes' exposure to pure nitrogen (Fazekas et al. 1941).

The measurements on portal blood (fig. 1) are less simply interpreted than the measurements on arterial blood, since a certain amount of surgical trauma was unavoidable in making them. At their face value, they suggest that insufflation of oyxgen was more liable to provoke a fall than a rise in portal oxyhæmoglobin. This, if real, might be related either to the cooling effect of the gas stream promoting vasoconstriction and stagnation of the blood in the lining of the stomach and intestine, or possibly to venous obstruction resulting from distortion of the regional anatomical relations by distended viscera or the sampling catheter. But the gas had been previously warmed and humidified, and placing the tip of the catheter in the main vein caused no gross obstruction of the portal tributaries. These findings with regard to portal blood are at variance with those of Poupa et al. (1957), who observed an increase of the order of 25% in the oxygenation of portal hæmoglobin after introducing oxygen into the small intestine of rats.

In their experiments gas was deliberately excluded from the stomach by ligating the pylorus, and it is said not to have passed beyond the ileocæcal valve; moreover the gas was stationary, and was presumably under pressure greater than atmospheric, although this was not specified. Poupa et al. described a rise in portal oxyhæmoglobin after insufflation of oxygen, but they found a greater rise after using air, and even a "small and transitory" rise with nitrogen (though from their graph this seems to have been little less than that with oxygen, and air seems to have been rather more effective than oxygen). Direct measurement of the gas absorbed from the intestine in some animals suggested that oxygen disappeared whereas nitrogen did not, but the experimental arrangements which these workers used were so different from those in the present studies that inconsistency in the results is not wholly surprising.

These laboratory experiments were conducted under such different conditions from those encountered in the management of asphyxia neonatorum that it would clearly be improper to argue from them that clinicians should abandon a resuscitative method which might be beneficial. But the intragastric administration of oxygen is not entirely free from risk (Barrie 1959) and misplaced trust in its value may deter the search for more efficacious therapeutic procedures. Hence, any quantitative information casting doubt on the value of intragastric oxygen may perhaps incite its advocates to seek more definitive indications of its merits than are at present available.

Summary

Changes in the degree of oxygenation of arterial and portal blood were measured after intragastric administration of oxygen to hypoxic animals.

The changes resulting from intragastric oxygen were compared with those in the absence of treatment and those when air was substituted for oxygen.

Under the conditions of these experiments intragastric oxygen was not beneficial.

Thanks are due to Dr. R. H. Kay for allowing the use of data obtained in joint experiments and for his comments; to Mrs. A. S. Spencer, B.SC., and Miss P. J. Cosgrove for technical assistance; and to Mr. A. Austin and Mrs. O. Davenport for help with the figures.

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"Given that a community has provided itself with . . . productive scientific resources, its obvious duty is to make the most of them. From time to time issues will arise, sometimes practical, sometimes ethical or moral, sometimes even political. The members of the community must take the trouble to inform themselves, or to be informed, of the facts, and they must then decide the issue upon the facts and upon the facts alone, undeterred by the activities of any 'anti' group. Because of that leaning to the bizarre which motivates a proportion of the British people, 'anti' groups tend to play a disproportionate part in their decisions; these groups are often wealthy, often dangerously skilled in persuasive propaganda, and—worst of all—sometimes contain people distinguished in some walk of life, who ought to know better."—Sir JAMES LEARMONTH, Surgery and the Community (3rd Maurice Bloch Lecture). Glasgow, 1960.

NATURAL HISTORY OF 338 TREATED AND UNTREATED PATIENTS WITH STAPHYLOCOCCAL SEPTICÆMIA (1936–1955)*

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With a statistical analysis by PAUL WILLIS, PH.D., *Statistician, Institute of Agricultural Medicine, State University of Iowa*

BEFORE the discovery of specific treatment, staphylococcal disease accounted for only a small proportion of all infectious disease. As new treatments have brought other diseases under control, staphylococcal infection has become relatively commoner. Some have suggested that such infection is increasing in frequency (Collins 1956, Finland and Jones 1956, Smith 1958); but others have denied this (McDermott 1956, Hassall and Rountree 1959). Some physicians are pessimistic about the treatment of staphylococcal septicæmia, but recent results of treatment in our hospital have been encouraging.

Our experience (Godfrey and Smith 1958) has confirmed that of Finland and Jones (1956) that many of the serious staphylococcal infections in hospitals are acquired after admission.

We have carefully assessed the course and outcome of staphylococcal septicæmia with special regard to the onset of the disease and to the effects of treatment.

Plan of Study

Our cases were obtained both from the clinical records coded as staphylococcal septicæmia and from the necropsy records of the University Hospitals for the years 1936–55 inclusive. These hospitals have 776 beds for the care of indigent patients, and in addition 131 beds for private patients. The necropsy-rate in these hospitals has varied between 42% and 72% of all deaths in the twenty-year period. Blood-cultures were taken at most necropsies, except those on stillborns and victims of trauma.

In the necropsy cases a positive blood-culture was accepted as evidence of septicæmia only if the diagnosis of staphylococcal septicæmia was listed by the pathologist or if focal abscesses or confluent staphylococcal pneumonia were also found. Septicæmia was considered to have been present when staphylococcal bacteræmia had been accompanied by major symptoms or signs of infection.

Of a total of 73 cases in which single blood-cultures were positive, 6 were rejected as bacteræmia by an independent physician who reviewed their clinical records. Of the remaining 67 cases in which single cultures were positive 58% had positive cultures for hæmolytic *Staphylococcus aureus* from sites other than the blood.

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Age, Sex, and Incidence

Our series consisted of 338 cases of septicæmia, including 69 in which staphylococcal septicæmia developed during another fatal disease. These 69 cases will be referred to as cases of "secondary septicæmia" and the others as "primary septicæmia", and all 338 cases as the "combined series".

The sex ratio of males to females was 1·94 to 1, but there was a preponderance of females in the 0–9 and 40–49 age-groups (table I). In half of the large number of men over 70 the disease developed after prostate resoection. The fatality-rate did not differ significantly between the sexes (75·3% in males and 81·0% in females). In young males the fatality-rate was disproportionately low. In the 0–20 age-group the fatality-rate was 46·6% for males, compared with 71·1% for females. This difference is statistically significant, yielding a critical ratio of 2·49 with P=0·05. The series included only 3 Negroes.

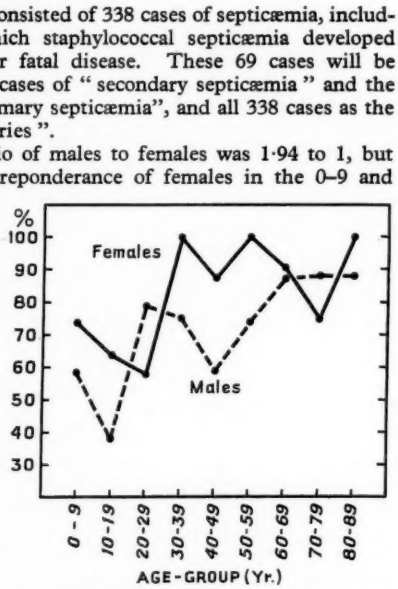

Fig. 1.—Fatality-rates in patients with primary staphylococcal septicæmia, according to age and sex.

The data of table I are shown graphically in fig. 1. When least squares best-fit lines are made, the increasing fatality with age in males is statistically significant (P=0·05), whereas in females it is not significant. The difference in the two slopes is also not significant.

That this is a disease of the extremities of life is clearly shown in fig. 2. Patients under 10 and over 69 made up 35·5% of the combined series. In other words, 120 cases fall outside the 10–69-year age-group, making a significant fraction of the total (χ^2 27·84 for a P of 0·001).

The overall fatality-rate of the combined series was 77·5%; but, excluding the deaths due to other causes, the corrected fatality-rate for primary staphylococcal septicæmia was 71·7% (table I). Among these cases of

TABLE I—AGE, SEX, AND FATALITY-RATE OF PATIENTS WITH STAPHYLOCOCCAL SEPTICÆMIA

—	Totals	0–9 yr.		10–19 yr.		20–29 yr.		30–39 yr.		40–49 yr.		50–59 yr.		60–69 yr.		70–79 yr.		80–89 yr.	
		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Combined series: No. of cases	338	28	37	34	15	20	13	15	4	14	11	29	12	37	14	33	8	13	1
Deaths	262	17	28	14	11	16	8	12	4	9	10	24	12	34	13	30	7	12	1
Primary septicæmia: No. of cases	269	26	34	32	11	19	12	12	2	12	8	19	9	25	11	25	4	8	1
Deaths	193	15	25	12	7	15	7	9	2	7	7	14	9	22	10	22	3	7	1
Fatality-rate (%)	..	58	74	38	64	79	58	75	100	58	88	74	100	88	91	88	75	88	100

primary staphylococcal septicæmia, 87 patients received no antimicrobial treatment. The death-rate in this group was 89·7%.

The annual incidence of staphylococcal septicæmia is shown in table II and fig. 3. From 1940 until 1950 there was a fairly steady decline, but thereafter the numbers rose.

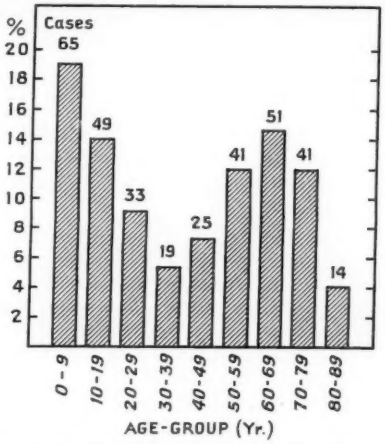

Fig. 2.—Age distribution of patients with staphylococcal septicæmia.

If at least squares best-fit line is made, there is no significant downward trend in the overall data; but when the data are analysed for 1936–44, 1945–51, and 1952–55, there is a statistically significant decline in the mortality for the last period.

The season of the year when each illness began was noted. The months of lowest incidence were July (22 cases), May (23 cases), and August (24 cases), and those of highest incidence were November (34 cases) and January, March, and April (32 cases each month). A χ^2 comparison of the three lowest-frequency months against the three highest yields a significant difference ($P=0{\cdot}05$).

Bacteriology

All but 5 of the combined series were caused by hæmolytic *Staph. aureus*. These 5 cases, which satisfied the criteria for the diagnosis of septicæmia due to *Staphylococcus albus*, together with 5 other cases not included here, have been discussed elsewhere (Smith et al. 1958a). At least 93% of the cultures taken during life were confirmed at necropsy.

At necropsy 14 cases of the combined series had gram-negative rods (proteus, coliforms, or pseudomonas), and 15 cases streptococci and gram-negative rods as well as staphylococci. Of 20 cases where there were more than ten cocci per ml., 19 were fatal.

In 70 cases diagnosed during life, three or more blood-cultures were taken. The first culture was sterile in only 14 cases; of these cases the second culture was positive in 8, the third culture in 5, and the fifth culture in 1.

Necropsy Findings

Necropsies were carried out in 327 cases (90·8% of the deaths in the combined series).

The *respiratory system* was the one most commonly involved. The most usual lesion was pneumonia. Recurring constantly throughout the necropsy reports is the phrase "hæmorrhagic necrotising pneumonia". Empyema was present in only 5 cases (3 were children) in a total of 107 pneumonias, but 3 further cases had sterile pleural effusions. 40 cases showed multiple pulmonary abscesses. 17 had septic emboli and infarcts of the lungs.

Multiple kidney abscesses were the commonest lesions of the *genitourinary tract* (39), and it was hard to separate from these those described as septic infarcts (14). There were 28 instances of pyelonephritis.

As regards the *cardiovascular system* there were 26 cases of endocarditis; 7 had rheumatic heart-disease and the others had arteriosclerotic heart-disease. Of 19 males and 7 females affected, 2 had infected mural thrombi. There was a relatively higher incidence of renal and cerebral lesions in the endocarditis series than in the combined series.

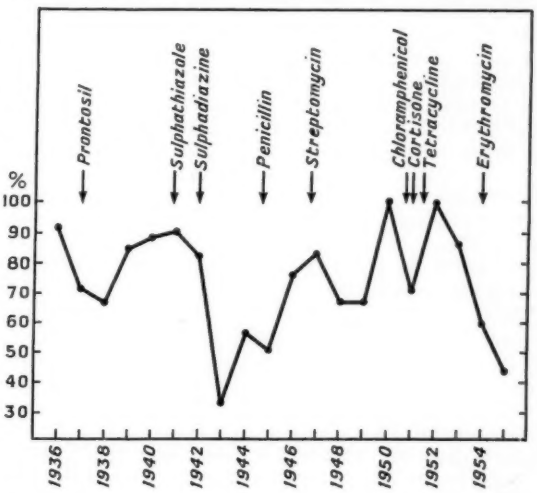

Fig. 3.—Fatality-rates, from staphylococcal septicæmia, 1936–55.

Myocardial abscesses were found in 18 cases, diffuse myocarditis in 2, and pericarditis in 14.

The findings in the *gastrointestinal system* included liver abscesses in 12, other abdominal abscesses in 13, peritonitis in 12, and enterocolitis in 9.

The findings in the *central nervous system* are incomplete because in 51 cases permission for examination of the

TABLE II—YEARLY INCIDENCE AND FATALITY-RATE OF STAPHYLOCOCCAL SEPTICÆMIA

—	Year: 19-																				Totals
	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	
No. of admissions ..	20,888	21,672	20,209	20,888	21,884	23,510	22,562	20,131	18,982	18,672	19,205	19,351	21,327	21,930	19,400	19,358	19,119	19,490	20,145	21,005	
Combined series ..	12	18	33	26	36	37	12	18	19	12	4	7	8	7	4	11	13	10	26	25	338
Deaths	11	14	23	23	32	34	10	8	11	7	3	6	6	6	4	9	13	9	18	15	262
Primary septicæmia	11	14	29	19	32	30	11	15	18	10	4	6	6	3	2	7	8	7	20	18	270
Deaths	10	10	19	16	28	27	9	5	10	5	3	5	4	2	2	5	8	6	12	8	193
Fatality-rate (%)	91	71	66	84	88	90	82	33	56	50	75	83	67	67	100	71	100	86	60	44	..

head was withheld. (In only 3 other cases were there any restrictions on the necropsy.) Meningoencephalitis was the main lesion found in 16 necropsies. There were 12 cases of cerebral abscesses, 3 of cerebral infarction, 2 of cavernous sinus thrombosis, and 1 of massive cerebral hæmorrhage.

There was a great variety of *skin lesions*, of which draining subcutaneous abscesses predominated. Petechiæ were found in 4 cases of endocarditis and also in 2 cases of aplastic anæmia without endocarditis.

Splenic abnormalities noted were "congestion" in 5, and infarction and a septic spleen in 25.

Bone lesions (in cases where these were sought) comprised only one focus in an upper limb, sixteen in the lower limbs, four in the spine, and six in the cranial bones.

Miscellaneous findings.—In a few cases there was destruction of the adrenal glands by necrosis (5) or abscesses (2). In addition to 4 cases of congenital cystic disease the pancreas showed lesions in 21 cases, the common lesion being fatty degeneration (9). Amyloid disease was present in 3 cases.

Lowered Host Resistance

53 of the patients had *malignant tumours*. Their death was probably hastened by the complicating septicæmia. A further 18 patients had *other potentially fatal diseases* such as myocardial infarction, aplastic anæmia, or fungus infection. In this group of 71 moribund patients the infection, which was almost without exception acquired in hospitals, gained entry through the genitourinary tract in 12 and through the respiratory tract certainly in 11 and probably in a further 13.

Diabetes (in 44 cases) we believe was no commoner in the group of patients than in our hospital population; but it was distinctly more common than in the general population (1·5%). There were no patients with recognised *influenza*. We draw particular attention to the frequency of *steroid therapy* (17 cases) as a predisposing cause; this treatment was given in 22·6% of the cases of septicæmia since 1951. The incidence of cases following transurethral resection of the prostate was lower in the second decade covered by the study than in the first: the great majority of such cases occurred before 1943.

These patients with lowered resistance make up 52·7% of the combined series. A miscellaneous group of 82 cases with lowered resistance from other causes included 35 which followed non-urological surgery.

Prognosis Related to Portal of Entry in Primary Septicæmia

The commonest early focus was the skin, the next commonest was the respiratory tract, then the bones and joints, and lastly an operative site. Infections originating in the respiratory tract or following surgery were the most likely to prove fatal. Whether treated or not, osteomyelitis cases proved less malignant than the others, but they did not appear to respond well to treatment. The respiratory tract as a portal of entry was commonest in children under 5 years of age, who made up 41% of this group. Children aged 5–15 years made up 62% of the septicæmias with bone as primary focus.

Among the untreated cases the only significant difference in fatality-rates was that of an unknown focus over a bone and joint focus. In the treated cases the fatality-rate was significantly greater when the disease began in the respiratory tract than when it began in skin, bones or joints, genitourinary tract, central nervous system, ear, or throat, or at an unknown site. Septicæmia originating from surgery or transurethral resection of prostate was significantly more often fatal than septicæmia from an unknown focus or bone and joint.

Duration of Disease in Fatal Cases

22 patients died after only one day or less in hospital, but most of them had a history of septicæmic symptoms for several previous days. Of the 22 patients who died within twenty-four hours after admission, 7 had acute bacterial endocarditis.

Untreated Cases

Of patients admitted before 1941 21% were treated with antimicrobial drugs, whereas subsequently only 21% did *not* receive antimicrobial treatment.

Among the patients not treated with antibiotics the fatality-rate was 85% in 40 who received blood-transfusions, compared with 96% in the remaining 47; this difference is not statistically significant. In the 23 cases not given antibiotics where intravenous glucose was given the fatality-rate was 96%, compared with 88% in the remainder; again the difference is without statistical significance.

In untreated patients the body-temperature, white-blood-cell count, and hæmoglobin did not correlate significantly with fatality.

The relation of fatality to age in untreated primary staphylococcal septicæmia is shown in fig. 4 and compared with similar data in treated cases. The older patients did not spontaneously recover, and the 10–19-year-old group had the lowest death-rate.

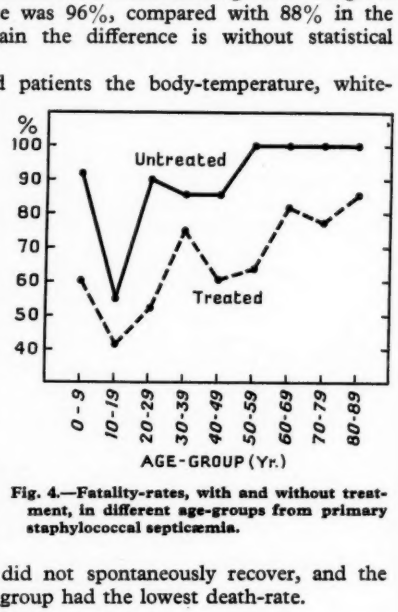

Fig. 4.—Fatality-rates, with and without treatment, in different age-groups from primary staphylococcal septicæmia.

Effect of Treatment

Study of deaths over the twenty-year period (fig. 3) suggests that mortality decreased as each new effective agent came into general use, but that with continued use the new agent lost its efficacy. There is a significant

TABLE III—FATALITY-RATE OF PRIMARY STAPHYLOCOCCAL SEPTICÆMIA WITH DIFFERENT FORMS OF TREATMENT

Treatment	No. of cases	Fatality-rate (%)
1. None	87	89·7
2. Sulphonamide alone	80	77·5
3. Penicillin alone	16	56·3
4. Sulphonamide and penicillin	31	32·3
5. Sulphonamide and penicillin plus*	16	50·0
6. Penicillin and tetracycline plus*	13	69·2
7. Miscellaneous	14	42·9

* Mostly streptomycin.

Treatments	P	*Treatments*	P
(1) v. (2)	0·075	(2) v. (6)	0·465
(1) v. (3)	...	(3) v. (4)	0·234
(1) v. (4)	0·024†	(3) v. (5)	0·472
(1) v. (5)	0·539	(3) v. (6)	0·490
(1) v. (6)	0·008†	(4) v. (5)	0·298
(2) v. (3)	0·112	(4) v. (6)	0·697
(2) v. (4)	0·719	(5) v. (6)	0·168
(2) v. (5)	0·472		

† Significant = $P < 0.05$.

TABLE IV—SITE OF ABSCESSES IN 22 CASES OF PYÆMIA

Site	No. of cases	Site	No. of cases
Kidneys	20	Abdomen ..	5
Myocardium ..	14	Adrenals	3
Lung	13	Bone	2
Brain	10	Subcutaneous ..	2
Liver	9	Skeletal muscle ..	2
Spleen	7	Miscellaneous ..	5
Acute bacterial endocarditis	7		

difference in fatality-rates between 1942 and 1943, and 1952 and 1954, but not between 1947 and 1948, 1951 and 1952, 1952 and 1953, or 1954 and 1955.

The results of various treatments singly and in combination are shown in table III and compared with the untreated series. The fatality was lower on regimens which contained both penicillin and sulphonamides. On each of the treatments there were more recoveries than could be expected on the basis of chance. Statistical analysis shows that penicillin alone, sulphonamides and penicillin, sulphonamides and penicillin "plus", and miscellaneous drug regimens were all superior to sulphonamides alone. Sulphonamides and penicillin were superior to penicillin and tetracycline "plus". No analysis was made of cases treated in accordance with in-vitro sensitivities.

Prognosis of Treated Cases.—Body-temperature and anæmia were not significantly correlated with fatality-rates. A maximum white-blood-cell count of over 20,000 per c.mm. was of bad prognostic significance. In 51 cases with an abnormal blood-urea-nitrogen the fatality-rate was 82%, and in 26 cases with a normal blood-urea-nitrogen it was 65%. In 52 cases this measurement was not recorded.

Pyæmia

22 of the cases had abscesses in three or more organs —notably the kidneys and myocardium with sparing of the lungs (table IV). All age-groups were affected except young adults aged 10–19. 4 patients were diabetics and 5 others had serious concomitant disease—namely, lymphoma, ulcerative colitis, actinomycosis, perforated duodenal ulcer, and metastasising adenocarcinoma of the prostate.

Of the patients with pyæmia 3 had *Escherichia coli* in their blood; in 3 others *Esch. coli* was isolated elsewhere in the body; and 7 others had likely sources of gram-negative bacillary infection, although no such bacteria were isolated. These sources included wounds from excision of carcinoma of the vulva and from transurethral resection of prostate, perforated rectum, perinephric abscess, and hæmorrhagic enteritis.

Discussion

Apart from a golden age between 1946 and 1950 the incidence of staphylococcal septicæmia was more or less the same throughout the twenty years from 1936 to 1955. It maintained a predilection for males over females in a ratio of 2 to 1 and was particularly common at the extremes of life. Our combined series is larger than others because of the care taken by our pathologists in studying necropsies. We believe that the incidence of this disease cannot be accurately assessed without bacteriological studies at necropsy. 91% (237) of our fatal cases were examined at necropsy. This constitutes 2·3% of the necropsies in this period.

When staphylococcal septicæmia is borne in mind, the diagnosis is not difficult. Fever, disorientation, and dyspnœa are common early symptoms. In some cases partial treatment may interfere with diagnosis. Tai and Hsieh (1957) found that 92·5% blood-cultures were positive when these are taken before specific treatment and 40·5% were positive when taken afterwards. If the organism cannot be isolated from the blood, urine or nasal cultures may prove positive and provide a guide to antibiotic sensitivity.

The large number of pulmonary lesions found after death suggests that the respiratory tract may be a common portal of entry, although in only 19% of our cases was this shown certainly to be the portal. Many patients receive transoral or transnasal catheter suction; and this may lead to severe pneumonia in nasal carriers of a hospital staphylococcus.

In patients with endocarditis staphylococcal septicæmia appears without warning and may begin with neurological symptoms or signs (Dowling et al. 1952, Fisher et al. 1955); the patient may die within a few days. In staphylococcal septicæmia without endocarditis petechiæ were rare, whereas in septicæmia associated with endocarditis they are common (Wilson and Hamburger 1957). Occasionally patients with endocarditis die rapidly, but it is rare for a patient with staphylococcal septicæmia uncomplicated by endocarditis to die rapidly. Although treatment must be started early and be guided by clinical experience of the antibiotic sensitivity of prevalent strains, these impressions should be confirmed by in-vitro testing, which must always be done.

The fatality-rate of the untreated cases in the present series corresponds with the rate in other published series (Baker and Shands 1939 [76%], Stookey and Scarpellino 1939 [91·4%], Hamburger and Ruegsegger 1941 [85%], Skinner and Keefer 1941 [82%], McLelland and Goldbloom 1942). The prevalence of hæmorrhagic necrotising pneumonia was striking. The time is past when a diagnosis during life or at necropsy of bronchopneumonia or lobar pneumonia is adequate. A precise bacteriological or virological diagnosis is essential.

Elsewhere (Smith 1956b) we have stressed the importance of host resistance, and so have others (McDermott 1956). The weak strain in a hospital patient who is only clinging to life may do more damage than a virulent strain in a healthy adult. Many of these lowered host resistance situations can be demonstrated and studied in mice (Smith and Dubos 1956a, b, and c).

A distressing number of infections were acquired in hospital. With the increasing proportion of older people and the increasing number of debilitated persons in the wards of our hospitals, control of infections must be more stringent (Smith 1958). In hospital, patients on adrenal steroids (Shaper and Dysen 1955) and debilitated patients should be watched carefully for signs of developing staphylococcal septicæmia. Transurethral resection of the prostate has been a dangerous operation with regard to subsequent septicæmia, but this danger seems to have decreased. Our experience agrees with that of others (Baker and Shands 1939, Stookey and Scarpellino 1939, McLelland and Goldbloom 1942) in that cases beginning with osteomyelitis were the least fatal.

Sulphonamides in our hands produced no significant improvement in the results of treatment (but see Herell and Brown 1941). Careful choice and use of antibiotics as indicated by in-vitro tests are essential for successful treatment. Experience in our hospital since this study was completed suggests that, when a correct diagnosis has been made and the antibiotic sensitivities of the strain

are known, the fatality-rate need not exceed 25% (Drevets and Smith 1960). Schirger et al. (1957) reported a fatality-rate of 34% using appropriate antibiotics. Tai and Hsieh (1957) report a fatality-rate of 31·3% in treated patients. We have discussed elsewhere the choice of chemotherapeutic agents (Smith 1957, 1958, Flocks et al. 1959). Treatment must be continued for at least four weeks. Antibiotics are poor weapons against established abscesses, and carefully planned surgery is still an essential part of treatment (Baker and Shands 1939, Tai and Hsieh 1957). As many cocci as possible should be removed mechanically: study of the multiplication of staphylococci in mice after inoculation by nine different routes showed that in all instances the mice died when a " critical lethal titre " of staphylococci had been reached no matter in which part of the body the cocci multiplied (Smith et al. 1958b).

The severity of cases originating in the respiratory tract or following surgery is evident. Others (Tai and Hsieh 1957) have indicated the poor prognosis of cases in coma. The number of bacteria per ml. of blood cultured is a useful guide to the seriousness of a case (Baker and Shands 1939, McLelland and Goldbloom 1942), and this test should be used more often. Young females and old males are particularly liable to die from staphylococcal septicæmia (MacNeal et al. 1942). Infections of the respiratory tract are least common in summer and autumn; and mortality from staphylococcal septicæmia is also lowest at these seasons. Blood-transfusions do not improve prognosis, and intravenous glucose does not worsen prognosis (as we had thought likely from our studies in mice (Smith and Dubos 1956b). A high white-blood-cell count is an ominous sign (Tai and Hsieh 1957). Anæmia in our series did not affect prognosis, which is contrary to the suggestions of others (Tai and Hsieh 1957). Anæmia in a patient with symptoms and signs suggesting septicæmia should alert the clinician to the possibility of staphylococcal infection. The data on treatment show the effectiveness of penicillin alone or with sulphonamides or tetracycline in the period studied. This may no longer apply, and precise bacteriological diagnosis and in-vitro assessment of antibiotic sensitivities are essential.

Summary

338 cases of staphylococcal septicæmia at a single hospital in the years 1936–55 are reviewed. In 69 cases septicæmia developed during another fatal disease. The disease occurred in all age-groups, but it was commonest at the extremes of life. It affected males twice as frequently as females.

Untreated, this disease had a 90% fatality-rate. After 1950 the incidence rose, but the fatality-rate in treated cases fell.

In the vast majority of instances, the first blood-culture was positive. A series of three cultures should suffice for diagnosis. A high proportion of cases were not diagnosed before death.

At necropsy hæmorrhagic necrotising pneumonia was most often found. Endocarditis was found in 10% of the cases with staphylococci in the blood. The disease was most likely to prove fatal when staphylococci gained access to the body via the respiratory tract or as a post-operative complication.

Many patients succumbed to this disease when they were debilitated by other conditions. Administration of penicillin alone or with other drugs was the most effective treatment in the years 1936–55.

Our thanks are due to Dr. Emory D. Warner, professor and head of the department of pathology, for permission to study the pathology records of the University Hospitals; to Dr. J. Roger Porter, professor and head of the department of bacteriology, for the work in his department on which this study was based; to the staff of the record department, especially Mrs. Dolan and Mr. William Emanuel, for their untiring assistance in searching for the many case-histories; and to Dr. William B. Bean, Dr. Morton Hamburger, and Dr. Franklin H. Top for their criticism and improvement of our manuscript. The errors that remain are our own.

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Addendum

Since this paper was written a series of papers on staphylococcal bacteræmia has been published in *Ugeskrift for Læger* (1959, **121**, 1593–1614) from the State Serum Institute and the Blegdamshospital in Copenhagen. The conclusions are similar to those expressed here.

ANTIFIBRINOLYTIC ACTIVITY AND METABOLISM OF Σ-AMINOCAPROIC ACID IN MAN

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IN 1957 workers in Japan found that Σ-amino-*n*-caproic acid (A.C.A.) is a plasmin inhibitor in vitro which is useful in inhibiting proteolytic enzymes in vivo. They gave A.C.A. in doses of 10–20 g. per day, by mouth and intravenously, to a hundred and twenty-one patients, and observed no toxic effects. They considered that the drug was remarkably effective against emesis gravidarum, dysmenorrhœa, threatened abortion, toxæmia of pregnancy, and various allergic disorders. But, although some of these conditions are thought to be associated with

increased plasmin activity, no attempt was made to detect fibrinolysis. Later Ablondi et al. (1959) and Alkjaersig et al. (1959) showed that in vitro A.C.A. acts primarily as a potent inhibitor of plasminogen activation.

One of us (I. M. N.) has systematically investigated a large number of clinical coagulation defects. In recent years we have found 43 cases with severe fibrinolysis as the cause of hæmorrhagic symptoms. Hence we wanted to know whether A.C.A. would effectively control fibrinolysis in man. We therefore studied the effect of A.C.A. on the blood-fibrinolytic system in seven patients, two of whom had pronounced fibrinolysis. Since the fate of A.C.A. in the body was not known, we also measured the rate of its disappearance from the plasma, and the amount excreted in the urine.

Methods

With the exceptions described below, the methods of collection and preparation of blood, and of measuring the different coagulation factors, were those of Nilsson et al. 1957a and b.

Assays of Fibrinolytic Activity

Whole-blood-clot lysis.—Samples of spontaneously clotted whole blood were incubated at 37°C in a water-bath and the time taken for complete lysis was recorded.

Plasma-euglobulin-clot lysis was performed as described by Sherry et al. (1959b).

Fibrin-plate method.—Fibrinolytic activity was determined on unheated and heated fibrin plates by the methods of Astrup and Müllertz (1952) and Lassen (1952) with modifications. Bovine fibrinogen prepared according to the glycine method of Blombäck and Blombäck (1956), with a coagulability of 97–98%, was used in a final concentration of 0·1% in Tris buffer of pH 7·8 and ionic strength 0·15. The fibrin plates were prepared in 'Plexi' glass dishes (diameter 11·8 cm.) using 28 ml. of the fibrinogen solution, clotted by the addition of thrombin solution ('Topostasine', Roche) 0·2 ml. containing 100 N.I.H. units per ml. Exactly 0·03 ml. of the solution to be tested was added as a drop to the clotted surface. Undiluted citrated plasma was usually used, and care was taken that the plasma was added to the plates within 30 minutes of withdrawing the blood. We observed considerable decrease in activator and plasmin activity of plasma after freezing or after 1–2 hours' storage at room temperature. The plates were incubated for 18–20 hours at 37°C, and the lytic activity was recorded as the product of two perpendicular diameters (sq. mm.) of the lysed zones (average of three determinations). Because bovine fibrinogen contains plasminogen the lysis recorded on the standard unheated fibrin plates measures the combined activity of plasminogen activator and plasmin in the sample. Plasmin alone was measured on heated fibrin plates, where the plasminogen was destroyed by heating to 85°C for 45 minutes. The lytic activity (unheated plates) of normal plasma varies between 0 and 70 sq. mm.

Serum Inhibitors of Plasminogen Activation

Blood was collected in ordinary glass tubes and allowed to clot. 2 hours later the serum was separated by centrifugation at 2000 g. for 25 minutes, and then stored at −20°C until required. The inhibitory effect of serum on plasminogen activation by streptokinase was studied in a clot system of pH 7·4 at 37°C. Human fibrinogen ('Kabi') with a coagulability of 95% was used. A highly purified streptokinase preparation containing 500 units per μg. nitrogen was obtained from Kabi Ltd., Stockholm. Each tube contained the following components in order of addition: 0·5 ml. serum of various concentrations + 0·2 ml. of 1% human fibrinogen in Tris buffer of pH 7·4 + 0·1 ml. streptokinase solution of various concentrations (50, 100, 200, 300, 400, 500, or 1000 units per ml. 0·9% NaCl) + 0·2 ml. thrombin solution (10 N.I.H. units per ml. 0·9% NaCl). The lysis-time was determined from when the streptokinase was added. Assays conducted at a final streptokinase concentration of 30 units per ml. reaction mixture usually showed the differences in inhibitory activity of the serum samples most clearly. In each case various concentrations of A.C.A. were added to the serum collected immediately before administration of A.C.A. These samples were assayed in the above test system (using a final streptokinase concentration of 30 units per ml.). The lysis-times were plotted on a graph, and from this curve the A.C.A. concentration in the serum samples collected after giving A.C.A. could be roughly calculated.

Determination of A.C.A. in urine.—The method, already described in detail (Sjoerdsma and Hanson 1959), comprised isolation of A.C.A. by high-voltage paper-electrophoresis, development of colour with ninhydrin and copper-spray reagents, elution of the spots from paper, and measurement in a spectrophotometer.

Method of A.C.A. administration.—The A.C.A. was a commercial preparation from Messrs. Light & Co., Colnbrook, Slough, Bucks. For intravenous use a 5 or 10% sterile solution of A.C.A. in saline was infused over 15–30 minutes. Oral doses of A.C.A. were given as a drink, 6 g. being dissolved in 200 ml. of mineral water.

Clinical Data

The antifibrinolytic effects of A.C.A. were studied in three patients; two (cases 1 and 2) had clinically significant fibrinolysis, and one (case 3) had an increased plasma level of plasminogen activator. The metabolism of the drug was studied in four other subjects (cases 4–7).

Case 1.—A man of 73, in the terminal stages of hepatic cirrhosis, with ascites, œsophageal varices, and cerebral confusion, had an increased bleeding tendency, and several large hæmatomas. The serum-bilirubin was 5·1 mg. per 100 ml. Increasingly severe fibrinolysis had been observed for a month, during which the fibrinogen value had decreased from 0·16 to 0·04 g. per 100 ml.

Coagulation studies immediately before A.C.A. was given on July 7, 1959, showed: coagulation-time, 12 min.; bleeding-time, 2 min.; platelet-count, 132,000 per c.mm.; prothrombin and proconvertin (Owren's P and P), 23%; factor V, 36%; plasma-antihæmophilic-globulin (A.H.G.) activity, 80%; and plasma-hæmophilia-B-factor activity, 14%. The plasma-antithrombin activity was increased. The fibrinogen was 0·04 g. per 100 ml. and the whole-blood-clot lysis-time was 1 hour (normal value >24 hours). The fibrinolytic activity of plasma was 348 sq. mm. on unheated plates, and 120 sq. mm. on heated plates. The euglobulin-lysis-time was 25 min. The plasminogen+proactivator content of the plasma was 20% of normal, and the inhibitory activity of serum on plasminogen activation was decreased also.

After A.C.A. was added to the blood, the plasma was assayed

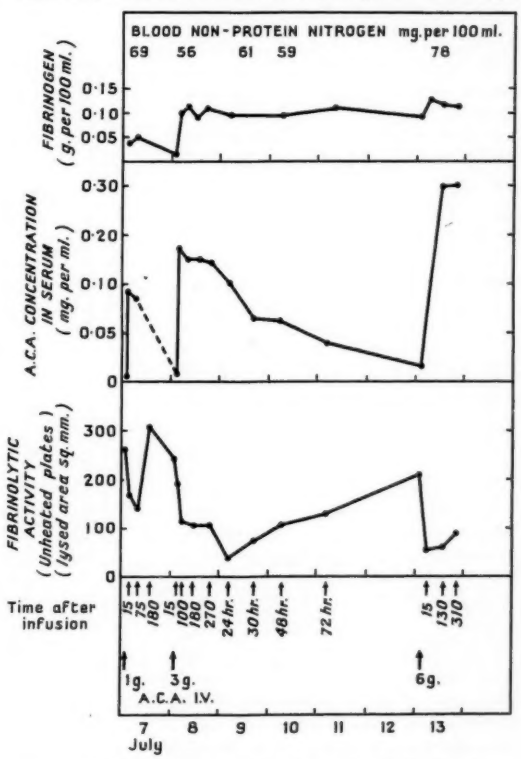

Fig. 1—Effect of giving A.C.A. intravenously in case 1.

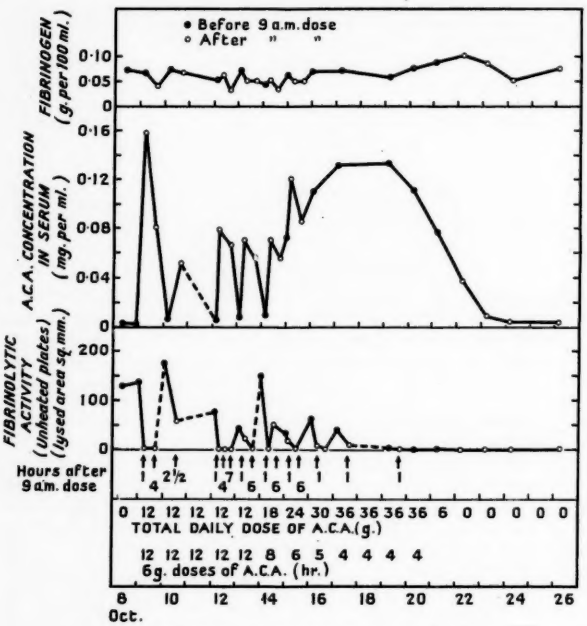
• Before 9 a.m. dose
○ After " "
FIBRINOGEN (g. per 100 ml.)
A.C.A. CONCENTRATION IN SERUM (mg. per ml.)
FIBRINOLYTIC ACTIVITY (Unheated plates) (lysed area sq. mm.)
Hours after 9 a.m. dose
TOTAL DAILY DOSE OF A.C.A. (g.)
6 g. doses of A.C.A. (hr.)
Oct.

Fig. 2—Effect of giving A.C.A. by mouth in case 2.

for fibrinolytic activity on unheated fibrin plates. Plasma without A.C.A. gave a zone of 348 sq. mm., while plasma with A.C.A. (0·5 mg. per ml. blood) gave a zone of 203 sq. mm. This indicated that both plasmin and activator were present in the patient's plasma.

The patient was given A.C.A. intravenously in doses of 1, 3, and 6 g. on July 7, 8, and 13 respectively. The results of studies on the fibrinolytic system are shown in fig. 1. Other coagulation factors were also measured, but no changes were observed. In the interval between the second and third doses of A.C.A. the patient went into hepatic coma, and he died on July 14. Necropsy showed hepatic cirrhosis and generalised arteriosclerosis. Microscopy of the kidneys did not reveal any abnormality.

Case 2.—A man of 61, with acute promyeloblastic leukæmia, had hæmaturia, melæna, and many large hæmatomas on different parts of the body. Coagulation studies before A.C.A. was given showed: coagulation-time, 10 min.; bleeding-time, 24 min.; platelet-count, 72,000 per c.mm.; prothrombin consumption, 120%; prothrombin and proconvertin (Owren's P and P), 59%; factor V, 44%; plasma-A.H.G. activity, 43%; plasma-hæmophilia-B-factor activity, 70%; and fibrinogen, 0·07 g. per 100 ml. The whole-blood-clot lysis-time was 15 min., and the euglobulin-lysis-time was 13 min. The fibrinolytic activity of plasma was 140 sq. mm. on unheated plates, and 80 sq. mm. on heated plates. The plasminogen+proactivator content of the plasma was 42% of normal. The inhibitory activity of serum on plasminogen activation was decreased.

The patient was given A.C.A. by mouth for 13 days, beginning with a daily dose of 12 g. which was successively increased to 36 g. (fig. 2). When the daily dose of A.C.A. reached 24–36 g. the hæmaturia and melæna ceased, and the hæmatomas diminished in size and no new ones appeared. The results of studies on the fibrinolytic system are given in fig. 2. Other coagulation factors were also measured. Except that the A.H.G. level increased to 75%, no changes were observed. The blood non-protein nitrogen (N.P.N.) was 36 mg. per 100 ml. before giving A.C.A., and 90 mg. per 100 ml. afterwards. The leukæmic blood-picture was not affected. Despite control of bleeding, the patient's condition deteriorated rapidly, and he died from circulatory insufficiency and bronchopneumonia 6 days after withdrawal of the drug. Necropsy showed myeloblastic leukæmia. Punctate hæmorrhages were demonstrated in the brain and pericardium. The kidneys appeared normal on gross and microscopic examination.

Case 3.—A woman of 81 with cerebral atherosclerosis and encephalomalacia was confined to bed because of hemiplegia. She had no signs of bleeding. The blood-N.P.N. was 42 mg. per 100 ml. Coagulation analyses showed the plasma to have an increased activator activity (lysed zone on unheated plate 290 sq. mm., and on heated plate 0), but no whole-blood-clot lysis occurred, and the euglobulin-clot lysis-time was >20 hours. The fibrinogen value was 0·66 g. per 100 ml., and the other coagulation factors showed normal values. The patient was given four intravenous doses of A.C.A. 6 g., and one dose of 3 g., between July 7 and Aug. 14, 1959. The subsequent changes were restricted to the fibrinolytic system (fig. 3). The blood-N.P.N. value did not increase. A month after the last dose of A.C.A. the patient died from bronchopneumonia. Postmortem studies, both macroscopic and microscopic, did not reveal any "toxic" changes.

Case 4.—A 51-year-old woman (weight 51 kg.) had psychoneurotic symptoms but no apparent organic disease. Investigation of coagulation factors revealed no abnormality. The patient was given A.C.A. 6 g. intravenously, and 3 days later 6 g. by mouth.

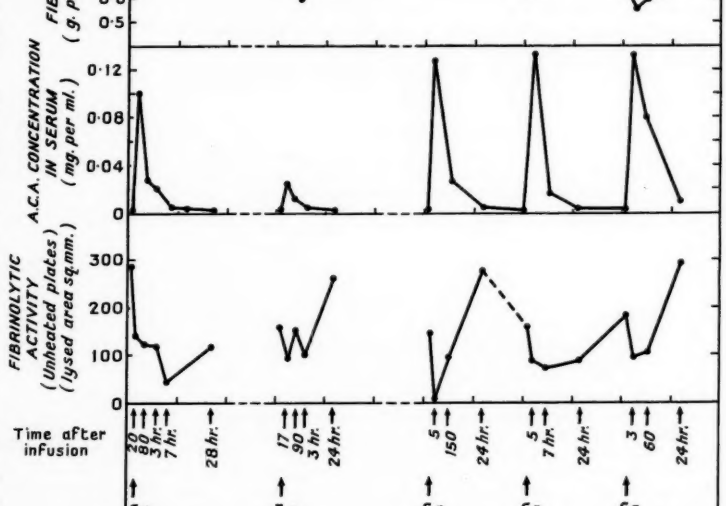

Fig. 3—Effect of giving A.C.A. intravenously in case 3.

SERUM INHIBITOR LEVELS AS A.C.A. EQUIVALENTS (MG. PER ML.) AFTER SINGLE INTRAVENOUS AND ORAL DOSES

Case	Dose (g.)	Route	After A.C.A. (mins.)				
			30	60	120	180	300
4	6	I.V.	0·28	..	0·02	..	0·01
	6	Oral	0·10	..	0·20	..	0·04
5	6	I.V.	..	0·12	0·09	0·08	0·06
	6	Oral	..	0·11	0·12	0·12	0·08
6	6	I.V.	..	0·12	0·08	0·05	0·02
	6	Oral	..	0·22	0·19	0·14	0·05
7	6	I.V.	0·14	0·13	0·10	0·08	0·03
	6	Oral	0·14	0·38	0·28	0·19	0·08

I.V. = intravenous.

Cases 5 and 6.—These patients were men of 51 (weight 77 kg.) and 52 (weight 62 kg.). Both had healed peptic ulcers, and their coagulation was normal. They were given A.C.A. 6 g. intravenously, and 6 days later 6 g. by mouth.

Case 7.—A man of 58 (weight 80 kg.) had uncomplicated hypertension and normal coagulation. A.C.A. 6 g. was given intravenously, and 4 days later he had 6 g. by mouth.

Results

The effect of A.C.A. in case 1 is shown in fig. 1.

75 minutes after an intravenous dose of A.C.A. 1 g. the fibrinolytic activity, as measured on unheated fibrin plates, decreased from 250 to 140 sq. mm., and the inhibitory activity of serum, expressed in A.C.A. equivalents, was 0·08 mg. per ml. After 3 hours the fibrinolytic activity and the inhibitory activity of serum had returned to the control values.

Next day the patient was given A.C.A. 3 g. intravenously. As fig. 1 shows this dose was followed by a significant decrease of the plasma-fibrinolytic activity as determined on fibrin plates. The whole-blood lysis-time increased from 1 to 24 hours, and the plasma-euglobulin-clot lysis-time from 25 to 100 min. In addition, the fibrinogen level increased from 0·01 to 0·11 g. per 100 ml. The inhibitory activity of serum was equivalent to 0·18 mg. A.C.A. per ml. This dose was still effective after 24 hours.

During the next 3 days the inhibitory level fell to the original value, and concomitantly the fibrinolytic activity of the plasma increased. The patient was then given a further intravenous dose of A.C.A. 6 g., which again controlled the fibrinolysis and increased the inhibitory activity of serum to a level corresponding to 0·30 mg. A.C.A. per ml. serum. His tendency to hæmatoma formation seemed to diminish. The fibrinogen level increased with treatment from 0·01 to 0·12 g. per 100 ml., and this may be interpreted as a consequence of a longer survival-time of the circulating fibrinogen because of less fibrinolytic activity.

Fig. 2 shows the effect of oral A.C.A. in the patient (case 2) with acute leukæmia and severe bleeding due to fibrinolysis.

One dose of 6 g. caused a significant decrease of fibrinolytic activity as measured on both unheated and heated plates. The effect could be detected as early as 30 minutes after ingestion of the drug. The whole-blood-clot lysis-time ranged between 5 and 12 hours after the drug was given, whereas it had been between 15 and 20 minutes before; corresponding values for the plasma-euglobulin-clot lysis-time were 60 and 13 minutes. The effect of one oral dose of A.C.A. 6 g. lasted for 4–5 hours.

When the inhibitory activity of serum began to decrease to values below 0·06 mg. A.C.A. per ml. the fibrinolytic activity increased. For this reason the oral dose was increased successively in order to keep the inhibitor activity high and the fibrinolytic activity low or negligible. This was not achieved until the total daily dose had reached 36 g., given as 6 g. doses 4 hourly. As can be seen from fig. 2 the fibrinolytic activity then disappeared, and the inhibitory activity in serum remained at 0·1–0·14 mg. per ml. in A.C.A. equivalents. The fibrinogen level only increased from about 0·05 g. per 100 ml. to 0·12 g. per 100 ml. The bleeding symptoms ceased when huge doses of A.C.A. were given, showing clearly that the drug was effective. Altogether, this patient received 282 g. of A.C.A. over 13 days.

Fig. 3 shows the effect of giving A.C.A. intravenously to case 3.

This patient had a high activator content in the plasma, but no plasmin activity. After the first intravenous dose of 6 g. A.C.A. had been given the activator activity decreased from 280 to 50 sq. mm. as measured on unheated fibrin plates. The inhibitory activity in serum reached 1 mg. per ml. A.C.A. equivalents after 20 minutes, and returned to control levels within 7 hours. Three further doses of A.C.A. 6 g. gave similar results.

The overall metabolism of the drug in the body was evaluated by bioassays of "inhibitor" levels in serum and chemical measurements of unchanged drug in the urine. The results of serum assays in four cases after oral and intravenous doses of A.C.A. 6 g. are shown in the table. Where the drug was given by mouth the levels approximated or exceeded those which followed the corresponding intravenous dose in each case. This suggests that absorption from the intestinal tract is rapid and essentially complete. While the data do not permit precise estimation of plasma half-life, it appears to be short—i.e., in the order of 1–2 hours. A large proportion (40–60%) of a single dose of A.C.A. was recovered in the urine within 12 hours, and only a small amount (2–4%.) was excreted during the second 12 hours. The values for 12-hour excretion in cases 5 and 6 were 4·9 and 3·9 g. after intravenous administration, and 4·2 and 3·4 g. after oral administration. In case 2, during the 5 days when 6·0 g. of A.C.A. was given every 12 hours, the amount excreted in the urine was 3·8–5·8 g. per 12 hours. The urinary excretion figures also indicate efficient absorption of the drug from the intestinal tract, and show that the primary means of disposal of A.C.A. is by renal excretion.

The patients tolerated the drug remarkably well, even in full dosage. During intravenous infusion no alteration in blood-pressure, pulse-rate, or respiration, and no subjective complaints were encountered.

Discussion

Enhanced fibrinolysis has been reported in various diseases. With the possible exception of abruptio placentæ with defibrination of maternal blood, pathological fibrinolysis (e.g., in carcinoma of prostate, hepatic cirrhosis, leukæmia, obstetric complications, or after pulmonary surgery or extracorporeal circulation) most probably arises from increased circulating levels of plasminogen activator (see reviews by Astrup [1956] and Sherry et al. [1959a]). While the symptoms are often slight (easy bruising, purpura, &c.), and accompanied only by mild hypofibrinogenæmia, patients often present with afibrinogenæmia and severe hæmorrhage which does not respond to the usual therapeutic measures. Fibrinogen, often given in large quantities in these circumstances, is usually without significant effect because of its rapid destruction by plasmin. Theoretically control of fibrinolysis by giving an inhibitor of plasminogen activation followed by the use of fibrinogen should be satisfactory. In these respects, A.C.A. is promising.

A.C.A. temporarily abolished pathological fibrinolysis in cases 1 and 2. The second patient also showed convincing clinical evidence of a therapeutic response during maintenance therapy with A.C.A., for his hæmaturia and melæna ceased. In case 3 great increase in the circulating level of activator in the absence of plasmin activity gave clear evidence of the inhibitory action of A.C.A. on plasminogen activator in vivo.

These studies show that relatively large doses (3–6 g.) of A.C.A. are needed to produce an effective level of inhibiting activity in the blood. Moreover, although the drug is equally effective whether given by mouth or intravenously, rapid urinary excretion necessitates that, for optimal effects, it must be given every 4–6 hours. This is not a deterrent to its use under emergency conditions for a few days. Whether more prolonged use of A.C.A. in adequate dosage (20–40 g. per day) is safe awaits further evaluation. Uræmia is a relative contraindication; in case 1, with an elevated blood-N.P.N., the effect of A.C.A. lasted longer than it did in the other cases. Post-mortem examinations in cases 1–3 showed no apparent toxic effects of the drug, but renal function should be watched closely when A.C.A. is given in large dosage for more than a few days.

Although A.C.A. seems to represent an important first step, in controlling excessive fibrinolysis it is hoped that more potent drugs with a similar action will be produced.

Summary

In short-term studies on two patients Σ-aminocaproic acid was effective in the treatment of pathological fibrinolysis. The effect of the drug in inhibiting plasminogen activation was shown in a third patient with increased circulating levels of activator in the absence of detectable plasmin.

Metabolic studies indicated efficient absorption of Σ-aminocaproic acid from the intestinal tract, but because of rapid urinary excretion doses of 3–6 g. must be given every 4–6 hours for optimal control.

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LEPTOSPIRA BRATISLAVA ISOLATED FROM A HEDGEHOG IN SCOTLAND

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LEPTOSPIRAL infections of hedgehogs have been reported in the U.S.S.R. by Ananin (1951, 1954), in Czechoslovakia by Kmety (1954, 1957, 1960), in Poland by Parnas and Dombrowski (1957), and in Roumania by Combiesco et al. (1959). Webster (1957) reported evidence of *Leptospira pomona* infections in 2 hedgehogs in New Zealand, and van der Hoeden (1958) described a survey in Israel where 44 of a total of 142 hedgehogs were found to be infected: strains of *L. canicola*, *L. grippotyphosa*, *L. mini*, and *L. ballum* were isolated.

During the spring and summer of 1959 we examined hedgehogs caught in the environs of Edinburgh for evidence of leptospirosis. In this survey, which is not yet completed, the kidneys of 1 hedgehog were found to harbour a strain of leptospire which is apparently identical with *L. bratislava*, the serotype which is most commonly found in hedgehogs in Czechoslovakia and which also occurs in these animals in the U.S.S.R. and Poland.

Materials and Methods

The hedgehog (*Erinaceus europæus europæus*, Linnæus) was brought to the laboratory alive and was killed with chloroform. Heart-blood was withdrawn immediately for agglutination tests, and a specimen of urine was obtained from the bladder. The kidneys, which appeared swollen and darker than normal, were removed; and, after the surface had been seared with a hot scalpel blade, small particles were punched out with a Pasteur pipette and introduced into bottles of modified Stuart's medium (Bryan 1957). Two of the bottles were incubated at 37°C and two at 28°C.

Results

No leptospires were seen in the urine when it was examined by dark-ground microscopy.

The hedgehog serum gave the following results when tested against seven leptospiral serotypes (results expressed as the reciprocals of agglutination titres): *L. icterohæmorrhagiæ* 30, *L. canicola* negative, *L. pomona* 30, *L. grippotyphosa* 30, *L. sejroe* 100, *L. bataviæ* 100, *L. ballum* 30.

One of two kidney cultures incubated at 37°C was positive eleven days later. The strain was labelled "strain hedgehog 10".

Strain hedgehog 10 was not agglutinated by the hedgehog serum. It reacted to full titre with antisera *L. australis A* and *L. muenchen*; and there was also a high cross-reaction with *L. autumnalis* antiserum, which suggested a somewhat closer affinity with *L. muenchen*. However agglutinin-absorption tests showed that strain hedgehog 10 was neither *L. australis A* nor *L. muenchen*. The results are shown in the accompanying table.

ABSORPTION TESTS WITH STRAIN HEDGEHOG NO. 10

Antiserum	—	Titre against		
		L. australis A	*L. muenchen*	Strain no. 10
australis A ..	Unabsorbed	10,000	3000	3000
	Absorbed *muenchen*	3000	−ve *	−ve
	Absorbed strain no. 10	3000	300	−ve
muenchen ..	Unabsorbed	1000	3000	3000
	Absorbed *australis A*	−ve	3000	3000
	Absorbed strain no. 10	100	3000	−ve
Strain no. 10	Unabsorbed	300	1000	10,000
	Absorbed *australis A*	−ve	100	3000
	Absorbed *muenchen*	−ve	−ve	3000

* No agglutinin in dilutions of 1/50 upwards.

At this stage of identification the strain was sent to Dr. Emil Kmety, of Bratislava, who has carried out antigenic analysis of many strains related to *L. australis A* and has found that they can be differentiated into serotypes which together form an australis A group. (This work, reported in Lublin, Poland, in 1958, is in process of publication.) Kmety found by cross-absorption tests that our strain "hedgehog 10" was identical with the serotype *L. bratislava* of the australis A group.

Comment

Kmety (1960) reports that the first strains of leptospires isolated from hedgehogs, *Erinaceus europæus roumanicus*, in Slovakia in 1953 were found to form a new serotype within the australis A group. It was named *L. bratislava*.

* Dr. Broom died on March 16.

Later strains referred to as *L. erinacei europei* isolated by Ananin (1954) in the U.S.S.R. and by Parnas et al. (1958) in Poland were found to be identical with *L. bratislava*. In his survey of hedgehogs in Slovakia, Kmety found that 14 of 17 strains of leptospires isolated from the kidneys were identifiable as *L. bratislava* and that 35·4% of the hedgehog sera gave positive agglutination with that serotype with titres ranging from 1 in 100 to 1 in 50,000. It appears therefore that the hedgehog is the main host for *L. bratislava* in Eastern Europe. In a personal communication Kmety states that this strain has only once been isolated from another animal—viz., *Clethrionomys glareolus* (bank vole)—and once from the blood of a patient.

It is interesting that an identical organism has been found in a hedgehog in this country. A continuation of the survey will reveal to what extent hedgehogs carry this particular organism. How the infection was introduced it is difficult to say. Possibly the new serotype has emerged independently in both localities through adaptation to the hedgehog of strains of leptospires derived from other animal sources (Gsell 1949).

Until recently only *L. icterohæmorrhagiæ* and *L. canicola* had been identified in this country, but Broom and Coghlan (1958) showed that wild rodents were carrying other serotypes—viz., *L. ballum* and strains related to *L. saxkoebing* and *L. sejroe*. Another serotype can now be added to the list.

The fact that no antibodies for strain hedgehog 10 could be detected in the hedgehog serum is noteworthy. Similar observations were made during the rodent survey (Broom and Coghlan 1958) when mice harbouring leptospires in their kidneys were found to be negative in serological tests. Van der Hoeden (1958) reported only low serum titres for the homologous organisms in some hedgehogs from which leptospires were isolated, and in 1 hedgehog carrier of *L. ballum* no antibodies either for the homologous strain or for 16 other serotypes were found. These findings re-emphasise the importance of not drawing unwarranted conclusions regarding the prevalence of leptospirosis from surveys based on serological tests alone.

Summary

The first isolation of *Leptospira bratislava* in Britain is reported. It was cultured from the kidneys of a hedgehog caught near Edinburgh. This organism, which is closely related to *L. australis A*, is the type most commonly found in hedgehogs in Czechoslovakia.

I wish to thank Prof. J. W. Wolff, of the W.H.O./F.A.O. Leptospirosis Reference Laboratory, Royal Tropical Institute, Amsterdam, to whom I wrote for advice regarding the correct taxonomic placing of the hedgehog strain. Professor Wolff states that, although exact data of the serological investigation of "*L. bratislava*" have not yet been published, he believes, from the work already done, that the strain will ultimately be recognised officially as a distinct serotype.—J. D. C.

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Preliminary Communication

LYSOKINASE ACTIVITY IN ASCITIC FLUID

A PROTEOLYTIC enzyme capable of fibrinolysis occurs in normal blood as an inactive precursor, plasminogen, which is associated with the globulin fraction. An inhibitor, antiplasmin, is present in excess in the albumin fraction. Plasmin not only produces fibrinolysis but also digests other plasma-proteins, including fibrinogen.

The modes of activation of plasminogen are debatable, but for convenience in this communication, we use what Astrup [1] called the "activation scheme of 1954" (fig. 1).

Plasminogen can readily be activated in vitro by chloroform, which destroys antiplasmin; by techniques, such as fractionation of the plasma, which separate the plasmin-antiplasmin complex; and by the direct action of trypsin and of a tissue activator (fibrinokinase). Activation in vitro may also be achieved by streptokinase which converts a proactivator in the plasma to an activator, which in turn reacts with plasminogen to form plasmin.

1. Astrup, T. *Blood*, 1956, **11**, 781.

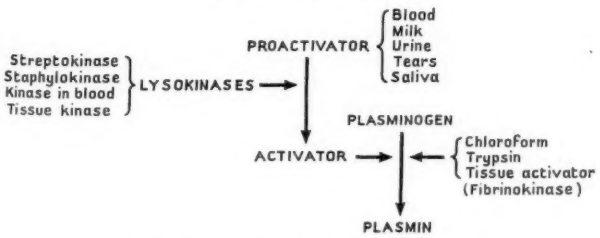

Fig. 1—Astrup's activation scheme of 1954.

Activation of plasminogen in vivo—which is referred to as spontaneous fibrinolysis—is highly complex, but in essence a proactivator present in the plasma is converted to an activator which, after clotting [2] converts plasminogen to plasmin. The way proactivator is converted to activator is unknown. The evidence for the existence of lysokinase is slender. A serum-lysokinase may be present in human and dog blood.[3,4] Attempts have been made to isolate active lysokinase from animal (including human) tissues, but in few instances have extracts shown measurable quantities of an agent with a lysokinase effect.[1]

In man [5–8] fibrinolytic activity can be induced within subcutaneous veins and arteries. The effectors have not been identified, nor is it known how they activate the fibrinolytic system in plasma. Efforts to determine the nature of the factor secreted have been thwarted by difficulties in isolating lysokinase and by lack of knowledge of its action, for lysokinase, according to the scheme presented above, might well be the factor. We knew that stimulation of veins seemed, at first sight, to produce two forms of fibrinolytic activity. One was very labile and required for its demonstration a low-temperature technique first used by Fearnley et al.[9] The other was relatively more stable, being due to an activator in the plasma. By a happy chance, while investigating antiactivator activity in

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hepatocarcinoma,[10] we found a rich source of what seems to be lysokinase.

MATERIAL AND METHODS

The supernatant of centrifuged blood-free ascitic fluid from abdominal paracentesis was used. With the exception numbered 12 below, the ascites had developed in seven patients with hepatocarcinoma complicating cirrhosis of the liver. Where appropriate, clotting was produced by adding 0·1 ml. of a solution of bovine thrombin (20 units per ml.) to the test system, which was observed frequently so that the time of complete lysis was noted. Other methods are more appropriately described below.

RESULTS

1. Ascitic fluid, 0·5 ml., was mixed with 0·5 ml. of citrated normal human plasma in a water-bath at 37°C, and the mixture clotted. All clots lysed. The mean lysis-time was $1{\cdot}5 \pm 0{\cdot}4$ hours.

2. To determine whether ascitic fluid contained plasmin, specimens of such fluid were applied to heated fibrin plates.[11] The fibrin was never affected. Lack of effect upon fibrinogen, casein, and gelatine provided additional evidence that plasmin was absent.

3. To exclude the possibility that ascitic fluid might contain plasminogen attempts were made to prepare chloroform-activated plasmin by the method of Rocha e Silva and Rimington,[12] as modified by Bidwell.[13] No plasmin activity could be detected in any specimen prepared.

4. Since bovine plasma contains very little, if any, proactivator the effect was tried of various amounts of ascitic fluid upon bovine plasma. No lysis was seen in any specimen in concentrations of ascitic fluid/bovine plasma ranging from 1/1 to 20/1. Hence we concluded that ascitic fluid contains neither activator, which converts plasminogen to plasmin after clotting, nor tissue activator, which converts plasminogen to plasmin directly.

5. To determine whether ascitic fluid contained proactivator or inactivated activator, 50 units of streptokinase in 0·5 ml. of saline were added to mixtures containing various amounts of ascitic fluid and bovine plasma. The ascitic fluid/bovine plasma ratio ranged from 1/1 to 20/1. In five specimens no lysis occurred. The other two underwent lysis when the ratio ascitic fluid/bovine plasma was 10/1 or more. These two exceptions were dropped from the succeeding observations.

6. The addition of human plasma in appropriate amounts, with its content of proactivator, to mixtures of ascitic fluid and bovine plasma resulted in lysis of the clot formed when thrombin was added. In the light of the scheme of activation set out above, the most reasonable interpretation is that the ascitic fluid has lysokinase activity.

7. Specimens of ascitic fluid were incubated at 37°C, 0·5 ml. samples were removed at intervals and mixed with 0·5 ml. of plasma, clotted, and watched for lysis. Fig. 2 shows the results.

8. To determine whether the addition of ascitic fluid to ice-cold plasma augmented the subsequent rate of lysis of the clotted mixture, 0·5 ml. samples of fresh ascitic fluid were mixed with 0·5 ml. of plasma in an ice-bath (A) or with 0·5 ml. of plasma at 37°C (B). Thrombin was then added to both tubes, and that in the ice-bath was transferred to the water-bath at 37°C. The mean lysis-time of A was $56 \pm 2{\cdot}6\%$ more rapid than that of B.

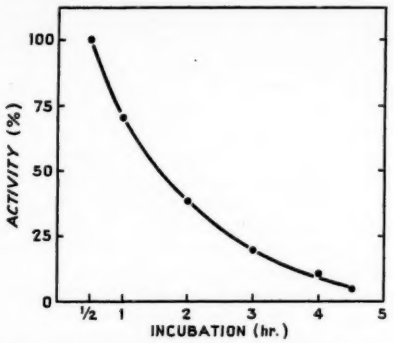

Fig. 2—Loss of lysokinase activity on incubating ascitic fluid at 37°C.
100% activity is that estimated 30 minutes after withdrawal of the ascitic fluid.

9. Ascitic fluid was concentrated by dialysis in a refrigerator at 2°C. While the activity of the dialysate in activating the fibrinolytic system in undiluted human plasma was greater, volume for volume, than that of the undialysed ascitic fluid, it was significantly less than was expected, indicating that, despite the low temperature, considerable activity had been lost.

10. Ascitic fluid dialysed as above was subjected to paper electrophoresis at 2°C, and eluates of the protein fractions were prepared using saline buffered to pH7·4. In two of five instances, when the eluate of the γ-globulin fraction was added to undiluted human plasma, the clot underwent lysis when thrombin was added. Addition of eluates of the other fractions had no lytic effect.

11. The observations numbered 7 and 8 suggested the presence of an antilysokinase in ascitic fluid and in plasma. Eluates of ascitic fluid were prepared as above and tested for antilysokinase activity. Ascitic fluid, 0·5 ml., was mixed with the eluate of the fraction under test, and allowed to stand in the water-bath at 37°C for 5 minutes. Plasma, 0·5 ml., was then added, and the mixture was clotted by thrombin. As a control the observations were repeated substituting buffered saline for the eluates. Eluates of the β-globulin fraction alone were active and had a striking inhibitory effect, but this was greatly reduced if the reagents were kept in an ice-bath before thrombin was added.

12. To find a more readily available source of activity observations were made on ascitic fluid from five patients with cirrhosis of the liver. The mean lysis-time of clotted mixtures of equal parts of ascitic fluid and plasma was $8{\cdot}4 \pm 1$ hours, which is significantly less rapid ($P = < 0{\cdot}001$) than that encountered in hepatocarcinoma. But, on the other hand, when streptokinase was added to mixtures of ascitic fluid and bovine plasma, one or more of the clotted mixtures lysed, although the ratio ascitic fluid/bovine plasma at which lysis occurred varied greatly. This finding is consistent with the presence of significant quantities of proactivator or inactivated activator, and we therefore temporarily abandoned our observations on ascitic fluid in cirrhosis.

COMMENT

It seems reasonable to conclude that a factor in the ascitic fluid associated with hepatocarcinoma (probably in

10. Kwaan, H. C., Lo, R., McFadzean, A. J. S. *ibid.* 1959, **18**, 252.
11. Astrup, T., Mullertz, S. *Arch. Biochem.* 1952, **40**, 346.
12. Rocha e Silva, M., Rimington, C. *Biochem. J.* 1948, **43**, 163.
13. Bidwell, E. *ibid.* 1953, **55**, 497.

the γ-globulin fraction) has lysokinase activity, and that the β-globulin fraction of ascitic fluid has antilysokinase activity. The rapid loss of lysokinase activity on incubation of ascitic fluid at 37°C indicates that, in vivo within the peritoneal cavity, lysokinase is continuously produced and destroyed. The source of lysokinase is unknown, but we have a promising lead in that a watery extract of the sediment of centrifuged ascitic fluid was found to be active. The source of antilysokinase seems to be the plasma; we have evidence that it is present in the β-globulin fraction, and that it may be β-lipoprotein.

The finding of proactivator or inactivated activator in the presence of lysokinase activity in two of the seven patients with hepatocarcinoma seems at first to be contradictory. This has also been encountered in streptokinase-activated human plasma, and it is discussed ably by Mullertz.[14]

The augmentation of fibrinolysis when mixtures of ascitic fluid and human plasma are clotted at low temperatures suggests that antilysokinase activity is reduced at low temperatures. This raises the possibility that the labile fibrinolytic activity encountered on stimulating veins, which is demonstrable by the low-temperature technique, may well represent the action of lysokinase which, at higher temperatures, would be at least partly inhibited. The more stable fibrinolytic activity, due to the activator, represents the action of lysokinase which has not been so inhibited. This possibility is supported by the finding of Greig and Runde[15] that in lipæmic plasma the β-lipoprotein fraction exerts an inhibitory effect upon labile fibrinolytic activity.

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14. Mullertz, S. *Acta physiol. scand.* 1956, **38**, suppl. 130.

15. Greig, H. B. W., Runde, I. A. *Lancet*, 1957, ii, 461.

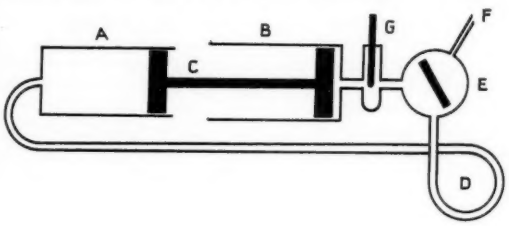
New Inventions

A DEVICE FOR CONTINUOUS MEASUREMENT AND RECORDING OF INTRAVASCULAR pH

WE have devised an instrument which allows the continuous measurement and recording of intravascular pH at constant temperature. The advantages over previous techniques [1] are: only semimicro quantities of blood are required, the subject need not be heparinised, and protein deposition on the glass electrode system does not seem to be troublesome.

The chemistry of the technique is based on observations by Hastings and Sendroy [2] and Van Slyke et al.[3] These workers found that, when blood was diluted 1:10 with neutral saline solution, the pH of the diluted blood was that of the original sample. The method was used for the spectrophotometric determination of pH of body fluids with phenol-red indicator.[3 4] Our instrument dilutes and mixes blood with neutralised saline in the proportions 1:10, and the pH of the diluted blood is measured in a microflow electrode system at a predetermined and constant temperature.

The mixing of blood and saline in fixed proportions is achieved by means of a special pump (see figure). Two 'Perspex' cylinders, A and B, are fitted with pistons having a common connecting rod C, which is screw-threaded. The connecting rod is driven by a worm-reduction unit without rotation of the pistons. The internal diameter of cylinder A is 2·00 in. and that of B is 2·10 in.; thus the volumes displaced are in the ratio 10:11. Neutral heparinised saline from cylinder A is delivered through a heat-exchanger D, to a small perspex mixing chamber E, which contains a polyethylene-coated iron rod driven by a rotating magnet. Blood enters the mixing chamber via a short polyethylene catheter F, and the diluted suspension leaves the mixing chamber and enters the microflow glass-electrode system G (Electronic Instruments Ltd., type SMF 23) from which it passes to the cylinder B. The glass-electrode system, reference electrode, and potassium-chloride bridge, together with the heat-exchanger D, are immersed in a water-bath maintained at 38°C.



Neutral saline is prepared as described by Van Slyke et al.[3] with the addition of heparin 10 i.u. per ml. The cylinder A, and the dead space of the components B, D, E, and G, are filled with neutral heparinised saline. A sterile catheter is inserted into an artery or vein, and the magnetic stirrer is set in motion. Pumping is then started, and when diluted blood enters the electrode system, pH readings are taken. The pH is determined by a 'Vibron' measuring unit, and an electrometer having high sensitivity and stability (Electronic Instruments Ltd., models C33B and 33B). The instrument is calibrated by phosphate buffers as described by Van Slyke et al.,[3] the pH of these being periodically checked against phthalate and borate standards.

The output from the electrometer is fed to a pen galvanometer (Record Electrical Company Ltd., Altrincham, Cheshire), which records the pH on moving paper. The laboratory-made recorder is fitted with other pen galvanometers (Associated Electrical Industries Ltd., London), which enable simultaneous electrocardiographic, electroencephalographic, and blood-pressure tracings to be made.

The validity and accuracy of the method has been assessed by measurements on blood samples equilibrated at 38° C and at known gas tensions. Experiments on the anæsthetised dog have shown that the device gives an accurate continuous assessment of the intravascular pH. For ordinary purposes, the flow-rate is adjusted to about 0·1 ml. of blood per minute, but, when very rapid changes in blood pH are expected, the rate is increased to avoid error due to the time-lag inherent in the dead space of the components E, F, and G. The results during anæsthesia and other conditions will later be described in detail.

We wish to thank our engineering colleagues and Messrs. Denholm, Rees & O'Donnell of Liverpool for constructing the pump unit. The work was supported by grants from the United Liverpool Hospitals research committee.

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1. Aschberg, S., Sonderlund, S., Tunell, R. *Scand. J. clin. Lab. Invest.* 1959, **11**, 114.
2. Hastings, A. B., Sendroy, J. *J. biol. Chem.* 1924, **61**, 695.
3. Van Slyke, D. D., Weisiger, J. R., Van Slyke, K. K. *ibid.* 1949, **179**, 743.
4. Van Slyke, D. D., Weisiger, J. R., Van Slyke, K. K. *ibid.* p. 757.

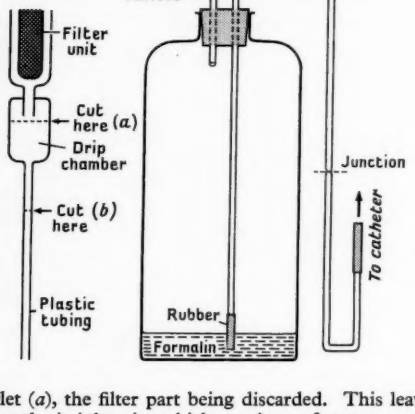
DISPOSABLE CLOSED DRAINAGE SETS IN UROLOGY

CLOSED drainage as a means of preventing infection in urological disorders—particularly those due to prostatic enlargement—has become well established.[1 2] Consequently a considerable load has been placed on theatre and sterilising staff in preparing, sterilising, cleansing, and resterilising apparatus. Hence we thought that time, trouble, and expense would be saved if the plastic transfusion sets used throughout much of the country could be adapted for closed urological drainage instead of being discarded. Our experience has been comparatively brief, but colleagues elsewhere have urged us to make our suggestions known.

In essence the requirements are:

1. Bottles of up to 2·5 litres capacity (commercial Winchester).
2. Bark corks to fit these bottles.
3. Discarded transfusion sets which have been washed through with cold tapwater (two required for each outfit).
4. A cork-borer no. 2.
5. A sharp knife or razor blade.
6. Sterilisable heat-sealing and non-sealing 'Cellophane', as used throughout the Blood Transfusion Service.
7. Formaldehyde solution *B.P.*
8. Paraformaldehyde tablets 1 g. (we have used 'Formogene').

As shown in the figure the cork is drilled in two places. The drip chamber to the transfusion set is cut off at the level of the



filter outlet (*a*), the filter part being discarded. This leaves a small funnel air-inlet, in which a piece of cotton-wool is placed. The plastic tubing is cut (*b*) so that when inserted through the cork about 1 in. protrudes from the lower end—i.e., the total length is about $2^1/_2$ in. The extension lengths of two sets, joined by the plastic needle mount, are then taken (giving a total length of over 8 ft.), and one end is passed through the second hole in the cork to extend almost the full depth of the bottle (about 12 in.). Since we find that the plastic tubing end is inclined to curl up, we add a rubber connector to give added weight. A second rubber connector on the proximal end enables it to be attached to the catheter. An ordinary plastic clip is placed close to the cork so that drainage can be restricted if necessary. The apparatus, now ready for sterilising (and to do this successfully the plastic tubing must be coiled in such a way that it does not kink), is wrapped in non-sealing cellophane and then in heat-sealing cellophane. For convenience we place two sets in each packet. They are sterilised in the autoclave at 15 lb. pressure for 30 minutes (without apparent deterioration of the plastic), and dried by drawing a vacuum in the ordinary way. The bottles are plugged with cotton wool, covered with greaseproof paper, and also sterilised in the autoclave.

1. Miller, A., Gillespie, W. A., Linton, K. B., Slade, N., Mitchell, J. P. *Lancet*, 1958, ii, 608.
2. Miller, A., Linton, K. B., Gillespie, W. A., Slade, N., Mitchell, J. P. *ibid.* Feb. 6, 1960, p. 310.

Before use 100–150 ml. of formaldehyde solution is placed in the bottle, and the cork and tubing are attached, the long tube being manipulated inside the bottle so that its end is below the surface of the liquid. A tablet of paraformaldehyde is put in the funnel air-inlet, and the open end of the long tube is attached to a glass tube placed in the catheter. The apparatus is now ready for use, but beforehand it is essential to check (1) that the clip is in the open position, and (2) that no serious kink is present. (About 1 in 40 of our sets has kinked in sterilisation, but this can be further reduced with practice.)

In our hands the set, including the bottle, has been replaced when the bottle has become full, not less often than once per day. We leave instructions that if a set becomes blocked by clot or debris no attempt should be made to clear it, but a fresh set should be used. In practice blockage seldom occurs.

A specimen of urine can be obtained without disconnection by shutting off the clip for a few minutes and then withdrawing urine through the rubber connector at the point of attachment to the catheter by means of a syringe and needle. Providing standard bottles are used, the output of urine can be measured by attaching a volume indicator as described by Miller et al.[1]

Wider adoption of our proposals would, we believe, help to reduce the incidence of bladder infection. The equipment is simple to prepare, and the basic requirements cost virtually nothing.

We are indebted to Dr. S. Vakil and Sister D. M. Courage, both of the Dorset County Hospital, for helpful and constructive criticism, and to Dr. G. H. Tovey, regional transfusion director, Southmead Hospital, Bristol, for urging us to write this account.

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AN ELECTRONIC NEONATAL RESPIRATORY MONITOR

APNŒIC attacks are common in the neonatal period and are a frequent immediate cause of death particularly in premature babies, in babies with cerebral irritation, and in babies with any form of respiratory difficulty. As their early detection is of the utmost importance, a special nurse is sometimes delegated to watch respiration. However, such special nurses are not always available, and their services are costly in terms both of cash and of time. The respiratory monitor is intended to replace the special nurse and to summon an attendant as soon as an apnœic attack occurs. During a six-month trial it has proved efficient and reliable, and on several occasions it has warned a special nurse, watching the baby, of a cyanotic attack of which she was unaware.

A detector is strapped across the upper part of the baby's abdomen and is connected to a transistorised circuit, controlling an alarm hooter. The circuit, batteries, and hooter are contained in a case $4 \times 4 \times 9$ in. To avoid false alarms caused by periodic breathing, the circuit is so designed that the alarm does

not sound for 15 seconds after the start of apnœa. As an attendant is not always present in the same room, an extension alarm is available which can be placed outside and is audible for a considerable distance.

The apparatus was made for me by Mr. W. L. Eaton, 81, Daville Avenue, Virginia, Durban, Natal.

Durban, Natal, South Africa W. E. B. EDGE M.B. W'srand, M.R.C.P., D.C.H., D.OBST.

Reviews of Books

General Anæsthesia

Vol. I. *Basic Principles*. Vol. II. *Techniques, Special Fields, and Hazards*. Editors: FRANKIS T. EVANS, M.B., F.F.A.R.C.S., D.A., anæsthetist, St. Bartholomew's Hospital, St. Mark's Hospital for Rectal Disease, and Royal Masonic Hospital, London; T. CECIL GRAY, M.D., F.F.A.R.C.S., D.A., professor of anæsthesia, University of Liverpool. London: Butterworth. 1959. Pp. vol. I 560, vol. II 460. 2 vols. 147*s*.

THIS is one of the best available books on general anæsthesia as a whole, aiming to provide postgraduates with a complete work of reference. The first volume deals with the basic principles of anatomy, physiology, and pharmacology, and the second with anæsthetic techniques in general and, very adequately and clearly, with many special branches of anæsthesia. There are some refreshingly brief and clear chapters on such hazards as explosions, other anæsthetic emergencies, and the anæsthetist's legal responsibilities.

The editors chose to ask specialists in each field to write the various chapters, and this plan is not without its disadvantages in a book designed for young anæsthetists studying for higher examinations. It is not easy for an anatomist to know precisely what anatomical knowledge is of most value to the anæsthetist, but it is surprising to find little reference to the anatomy of the veins and arteries of the arm in the chapter on anatomy.

Writers who are specialists in a particular subject cannot always assess how much specialised knowledge in their subject may be taken for granted (for example, the section on pharmacology talks of an " enolic tautomer " without a word of explanation; and how many anæsthetists really know what a quaternary nitrogen atom is?). The physiologist who tells anæsthetists that " the administration of pure oxygen to deeply anæsthetised cyanosed patients is not without danger " must expect many of them to be perplexed. The pharmacologist who talks of ether as a " chemically inert " substance will puzzle many who are looking for new non-inflammable anæsthetics for the very reason that ether can react with such chemical violence in the presence of a flame.

In an otherwise beautifully clear chapter on the relaxants it is a pity that the drugs are not dealt with consistently. For example, the pharmacology of *d*-tubocurarine is dealt with under the headings of Absorption, Excretion, Paralysant Activity, &c., but nothing is said of the absorption or excretion of gallamine. If nothing is known, this could usefully be stated. Several paragraphs are devoted to the M.R.C. blood bottles and giving-sets, but there is no mention of the now widely used disposable plastic sets. The chapter on anæsthetic apparatus could well be expanded, or else omitted altogether. As it stands, it is not sufficiently complete to meet the claims of the book. But these minor criticisms of the first volume detract little from the value of the book as a whole. Furthermore, the second volume has many chapters that are first-class examples of how a textbook should be written. The chapter on the types of congenital heart-disease will be read with delight and relief by many anæsthetists whose minds are not clear on the subject. Similarly, controlled hypotension is dealt with fully and clearly, without unnecessary elaboration. In the chapter on genito-urinary anæsthesia, it is a joy to be reminded that simplicity is still compatible with good anæsthesia, and that momentary apnœa may be produced without the need for repeated intravenous injections.

The book is not cheap, but it is outstandingly useful and well worth study by all who wish to keep up-to-date in anæsthesia.

The Discovery of Reflexes

E. G. T. LIDDELL, M.D., F.R.S., Waynflete professor of physiology, University of Oxford. London: Oxford University Press. 1960. Pp. 174. 30*s*.

THIS book is Professor Liddell's tribute to Sherrington, his friend and master. In the first four chapters he reviews the history of the physiology of the nervous system. First he describes the structural basis of nervous function and the technical devices, especially the increasing refinements of the microscope, needed for morphological study: this work culminated in the establishment of the neurone theory. Then the problems of function and the early studies of electricity in living tissues are reviewed: these findings prepared the way for an experimental approach to the nervous system. The book then turns to the classical experiments which established the Bell-Magendie doctrine of specific nerve energies, and Marshall Hall and Müller's views on the nervous arc and the activity of the spinal cord: the concept of reflex action was thus engendered. In the final chapter, which is the heart of the book, Sherrington's own large and fructifying contributions to the study of nervous function are reviewed up to the time of his Silliman lectures, subsequently published as *The Integrative Action of the Nervous System*.

Sherrington would have appreciated this book, for its balance, its lucidity, and especially its feeling for words. In the earlier chapters the byways of scholarship are entertainingly explored in illustrating the main theme. Old controversies and personalities are made to live again, but put in perspective by the author's dry comments. How irritating the brash young du Bois-Reymond must have been—the more so, because he was nearly always right! How familiar the contretemps over priority between Bell and Magendie and others. How pervasive the shadow of theological thought still was in the nineteenth century. The final analysis and appreciation of Sherrington—both his main work and " his customary diversions on subjects which he noticed as he passed along on his crusade of inquiry " —is equally well done.

This book can be recommended to the medical student as a pleasing introduction to the study of neurophysiology and to neurologists of all persuasions as a scholarly review of the historical background of this subject.

The Physiological Basis of Diuretic Therapy

ROBERT F. PITTS, PH.D., M.D., professor of physiology and biophysics, Cornell University Medical College, New York. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 332. 78*s*.

THE practitioner who can find time to read and digest this book will, as the author says in an introduction, gain much intellectual satisfaction from rational therapy rationally applied. It is one of the real pities of today that, despite our increasing understanding of health and disease, medicine is still so often empirical in its application, because the practitioner has so much to do and so little time for reading or thought. This book is in two parts, and the first admirably summarises and discusses our knowledge of the interrelationships between the fluid compartments of the body and their ionic constitution and balance. From this the book passes to a consideration of œdema formation, and the part played by the kidney in regulating water and salt balance. The author has a long acquaintanceship with renal physiology, and the chapters in this section are excellent summaries of present knowledge. Much of the information has not yet had time to reach the textbooks, and chapters IV, V, and VI might be recommended reading for medical students.

The second part of the book builds on these foundations and considers the action and therapeutic use of diuretic agents, which are divided into two classes, physiological and pharmacological. Each method of treatment and each drug are then considered in turn, with discussions of what they do and how,

and in what conditions they may do good. The book mentions doses, when substances should or should not be used, and how soon results may be expected, but it is not intended as a manual of treatment. It is meant to, and does, supply general principles and much interesting detail. At the end of each chapter there is a useful short list of references, and a summary which tempers the wind for weaker brothers. The diuretics considered range from the old-established digitalis glycosides, xanthines, and mercurials of many kinds through cation-exchange resins and steroids to the latest sulfonamyl diuretics. The last chapter deals briefly with some of the general complications of diuretic therapy. Throughout, the author writes with clarity and authority, and this book is highly recommended.

Diseases of the Skin

JAMES MARSHALL, M.D., head of the department of dermatology, University of Stellenbosch Medical School. Edinburgh: E. & S. Livingstone. 1960. Pp. 944. 84*s*.

THE author clearly set out to write a book devoid of the pious nonsense which convinces the student that dermatology is bogus. He has largely succeeded and it is safe to predict that his book will be popular: it reads well; it is topical, comprehensive, factual, and on the whole well illustrated. The author is a francophile and favours some unnecessarily odd nomenclature, always a bore to the student. More seriously, he adopts the curiously obtuse attitude of the French towards the psychological features of dermatology, denial of which does not abolish. In most other respects this is a good book.

Surgeon Compassionate

FRIEDA SANDWITH. London: Peter Davies. 1960. Pp. 235. 21*s*.

THERE hangs, in the board-room of the Royal Free Hospital, a picture which shows a young man, elegantly dressed in the style of a hundred and thirty years ago, supporting a young woman who lies in rags on a doorstep. The man is Dr. William Marsden, and the incident depicted is his encounter in 1828 with a woman who was mortally ill, but who could not gain entrance to any hospital without a letter of introduction from its Governor. It was that which prompted him to devote the rest of his life to the creation of a new hospital—one to which admission would be "free" in the most liberal sense of the word.

Dr. Marsden's great-granddaughter has now used the hospital minute-books and her family records to provide a very detailed and convincing account of his life. Her story is enhanced by much unusual information about Marsden's background, and about such people as the "Toshers" and "pure-finders", who were numbered so largely amongst his patients. ("Toshers" were sewer-hunters, who scavenged in the city drains; "Pure" was dog's dung which, being much in demand for tanning leather, was a very valuable commodity.)

The early years of the Free Hospital were troubled by dissension amongst its governors, and by some very hostile Press reports. On at least one occasion it incurred the wrath of Thomas Wakley, but it is pleasant to record that his son eventually became chairman of the hospital's committee of management, and that in 1867, when (after founding a second hospital) William Marsden died, *The Lancet* paid him unstinted praise as one who had done "signal service to mankind during his active and eventful life".

Henry E. Sigerist on the Sociology of Medicine

Editor: MILTON I. ROEMER, M.D., director of research, Sloan Institute of Hospital Administration, Cornell University. New York: M.D. Publications. 1960. Pp. 414. $6.75.

Henry Sigerist, considered by many to be the greatest medical historian of our time, possibly of all time, was born in Paris in 1891 and was attracted to the study of languages. By the time he was fifteen he was well versed in French, German, English, and Italian and was familiar with Greek, Latin, and Arabic. Later he added Hebrew, Chinese, and Sanskrit. Dissatisfied with the limits of philology he turned to science and finally to medicine, becoming deeply interested in its history. But his astute mind did not dwell only in the past. He was a visionary of immense range, looking well and wisely into the future and always with the historical background in mind. At the time of his death in 1957 he was engaged on an eight-volume history of medicine of which unhappily only the first two were completed. He had intended to follow this with a four-volume *Sociology of Medicine*.

The thirty-one essays in this book have been chosen from his abundant writings. None are available elsewhere in book form. They span a quarter of a century, from 1931 to 1955. Twenty-eight have been previously published but two are from manuscripts found among the Sigerist papers, and one is derived from an unpublished document submitted to the World Health Organisation. They have been arranged mainly on geographical lines—Europe, America, other lands, special topics, and a group of general essays. Much of the book is devoted to medical problems and trends in America.

Current Unrest in the Medical World and the other three essays devoted to Europe explore European medical programmes and their endeavours to meet the needs of an urbanised society. An Outline of the Development of the Hospital gives a short comprehensive history of the evolution of the modern hospital, and War and Medicine a dramatic account of the development of medicine in response to the demands of war. The Place of the Physician in Modern Society is a sweeping analysis of the changing role of the physician in a changing society. These are samples that show something of the scope of a book that is bound to interest medical and lay sociologists.

A Symposium on pH and Blood Gas Measurement. (London: J. & A. Churchill. 1960. Pp. 210. 30*s*.).—This volume reports one of the distinguished meetings arranged by the Ciba Foundation for a small group of participants, in this case apparently 25, though chapter V is credited to a contributor who is not listed as a participant. The objects of the gathering were "to exchange ideas on means of measurement, to discuss their clinical significance, and to consider how the abnormalities detected could be expressed most clearly to the clinician". In the book itself, the emphasis is very heavily on the first of these; and this is not at all a bad thing, for the analytical difficulties have been a major deterrent to the permeation of acid-base "know-how" into clinical medicine. The participants included scientific staff from the manufacturers of pH-meters, and ten of the 12 chapters are concerned with analytical methods. Of these surveys, that by P. Astrup, on ultra-micro-methods for determining pH, pCO_2, and standard bicarbonate in capillary blood, is outstanding; while J. W. Severinghaus looks perhaps more to the future in his account of electrodes capable of monitoring blood O_2 and CO_2. These analytical chapters are important not only for clinical chemists but also for anæsthetists and the operators of artificial hearts and respirators. While welcoming the implied tribute to a great clinical chemist, we note with mixed feelings the appearance of a new verb "to Van Slyke" with apparently a present participle "Van Slyking". The second objective, the discussion of clinical significance, crops up occasionally in discussion, and is the subject of a good short chapter by V. Wynn; and the third objective, making the clinician understand, receives only passing comment in the general discussion. The title in fact describes the contents more accurately than does the foreword; and within these limits this is an excellent book. It was edited by Prof. R. F. Woolmer, with the aid of Miss Joy Parkinson.

Recent Research in Freezing and Drying (Oxford: Blackwell Scientific Publications. 1960. Pp. 320. 63*s*.).—Living cells sometimes survive freezing and drying: how they may tolerate these extremes of physical environment has in recent years become a subject for detailed study. In this new book the editors, Dr. A. S. Parkes and Dr. Audrey Smith, themselves pioneers in this work, have collected a series of authoritative contributions based on papers given in London in 1958 by workers from many countries. The articles mainly concern the biophysics of these processes and their application to microbiology and to surgery. They can be thoroughly recommended.

THE LANCET

LONDON 18 JUNE 1960

Leptospirosis

KNOWLEDGE of the diseases caused in man and animals by leptospires has greatly increased in the past ten years. The scientific foundation was the isolation in Weil's disease of *Leptospira icterohaemorrhagiæ*, by Japanese [1] and German [2 3] workers in 1914 and 1915. Since then over forty types of leptospires have been distinguished by serological tests and have been found unevenly distributed over most of the temperate and subtropical countries of the world. In Nature these are parasitic on a very wide range of rodents, causing disease in them only occasionally. Leptospires are excreted in large numbers in the urine of infected rodents. Domestic animals—including dogs, pigs, cattle, sheep, goats, and horses—acquire leptospires from rodents or from one another and are much more prone than rodents to acute or chronic disease as well as to a carrier state with urinary excretion. Man becomes infected mostly from rodents but sometimes from domestic animals; transmission of infection from man to man has been very rare. In Great Britain infections in man have so far been found due only to *L. icterohæmorrhagiæ* from rats or *L. canicola* from dogs, and until recently these two types of leptospires were the only ones discovered in this country. In 1958, however, BROOM and COGHLAN [4] reported finding *L. ballum* in wood-mice and voles and leptospires related to *L. sejroe* and *L. saxkoebing* in voles in Scotland. An article in this issue on p. 1326 describes an investigation by the late DR. BROOM and by DR. COGHLAN of a leptospire from a hedgehog caught near Edinburgh. This strain is related to *L. australis A.* and *L. muenchen.* There may thus be unrealised sources of leptospirosis in this country.

In most countries of Europe, Asia, North and South America, and Australasia infections of man and domestic animals are commoner than in Great Britain, and they have been found due to several types of leptospires from a great variety of rodents; the concentration of the disease is greatest in Indonesia and Malaya, where about thirty infective types have been found. The occasions of infection everywhere are predominantly agriculture—especially harvesting cereals, sugar, rice, or vegetables—and the care of domestic animals on farms or at home. Nearly related circumstances arise in handling and preparing meat. Other occasions are mining, sewer and canal work, and bathing in fresh water. Man is infected usually by contact of skin, conjunctiva, or mucous membranes with leptospires from animals' urine, and less commonly by contact with infected animal tissues or bites by rodents or dogs. The disturbance ranges from severe hepatitis with jaundice, severe nephritis, meningitis, and general toxæmia to a mild febrile illness with or without obvious meningitis. Any of the types of leptospire may cause the milder disease, but the severe, possibly fatal, form is almost confined to infection by those types which commonly cause jaundice. Of these, *L. icterohæmorrhagiæ* is the most outstanding; but others, such as *L. andaman A*, *L. australis A*, *L. bataviæ*, and *L. pyrogenes* have caused severe and fatal infection.

After 1915 the subject was perhaps most intensively studied in Japan, the Netherlands and Indonesia, Andaman Islands, Malaya, Switzerland, Denmark, Germany, Russia, Italy, Australia, South America, France, and Great Britain. In the past decade much work has been done in Malaya, New Zealand, Israel, and the U.S.A. (Of the several monographs recording progress,[5–9] that by ALSTON and BROOM [9] is perhaps the most valuable.) In Malaya the infection was common among British and Asian soldiers in the guerilla warfare. MCCRUMB et al.[10] showed that leptospirosis accounted for 35% of all acute febrile illnesses among military personnel, and for 13% of the illnesses in 238 adult male Asian civilians investigated for the cause of pyrexia of unknown origin. TURNER et al.[11] have lately reviewed infections in Malaya, and in a further series found definite or suggestive serological evidence of leptospirosis in about 21% of 130 cases of undiagnosed pyrexia. EDWARDS and DOMM [12] name twelve types of leptospires causing disease in the U.S.A. The human disease was found to be associated with farming, veterinary and food-handling occupations, service in the Armed Forces, and bathing. In animals it produced abortion and loss of condition of cattle, pigs and sheep. These workers believe that meningitis will be found in 80-90% of all cases of leptospirosis if the cerebrospinal fluid is examined in the second week; the patient recovers completely regardless of management, and they agree with GSELL [7] that this meningitis reflects an antigen-antibody reaction.

With the growing recognition of this disease there has been much experimental investigation of the organisms and their effects on the animals which they invade. Electron micrographs [9] by J. D. FULTON and D. F. SPOONER have suggested fine details of cross-striation on the axial filament which twines round the main body of a leptospire; and this formation may be the site of the mechanism of motility. The types of leptospires—like most of the types of salmonella—show

1. Inada, R., Ido, Y., Hoki, R., Kaneko, R., Ito, H. *J. exp. Med.* 1916, **23**, 377.
2. Hübener, E. A., Reiter, H. *Dtsch. med. Wschr.* 1915, **41**, 1275; *ibid.* 1916, **42**, 131.
3. Uhlenhuth, P., Fromme, W. *Med. Klin.* 1915, **11**, 1202.
4. Broom, J. C., Coghlan, J. D. *Lancet*, 1958, ii, 1041.
5. Walch-Sorgdrager, B. *Bull. Hlth Org. L.o.N.* 1939, **8**, 143.
6. Rimpau, W. Die Leptospirose. Munich, 1950.
7. Gsell, O. Leptospirosen. Berne, 1952.
8. Austoni, M. Le Leptospirosi. Padua, 1953.
9. Alston, J. M., Broom, J. C. Leptospirosis in Man and Animals. Edinburgh, 1958.
10. McCrumb, F. R., Jr., Stockard, J. L., Robinson, C. R., Turner, L. H., Levis, D. G., Maisey, C. W., Kelleher, M. F., Gleiser, C. A., Smadel, J. E. *Amer. J. trop. Med. Hyg.* 1957, **6**, 238.
11. Turner, L. H., Elisberg, B. L., Gordon Smith, C. E., Broom, J. C. *Med. J. Malaya*, 1959, **14**, 83.
12. Edwards, G. A., Domm, B. M. *Medicine, Baltimore*, 1960, **39**, 117.

only small metabolic differences compared with their variety of antigens. Some leptospires have been analysed by SCHNEIDER [13 14]; ROTHSTEIN; and HIATT [15] concluded from ethanol extraction and dialysis that there were peripheral somatic antigens. The pathogenic mechanism of leptospires is far from fully understood, but FAINE [16] has suggested from culture of virulent and avirulent strains in different media and at different temperatures that the relative resistance of virulent leptospires to conditions resembling those in vivo may explain their survival in infected animals.

In severe infections the critical lesion is almost always an acute lower-nephron nephrosis similar to that sometimes found in crush injuries, burns, or incompatible blood-transfusions. These lesions may be due to vasoconstriction, but the mechanism is still uncertain. Oliguria and anuria with rise of blood-urea indicate their severity, and are a guide to the essential treatment, which is by the conservative régime of BULL [17] and, if necessary, the " artificial kidney ". Leptospirosis leaves very little damage in the kidneys, liver, or meninges in patients who recover (in dogs chronic and slowly fatal nephritis commonly develops). In contrast with the treatment of nephritis, antibiotic treatment of the disease is less important. All types of leptospire are sensitive to many antibiotic drugs, including penicillin, streptomycin, and the tetracyclines; but to be effective in experimental infection such treatment had to be started during the incubation period.[18] BROOM [19] showed that penicillin had not reduced the death-rate from Weil's disease in Great Britain up to 1950. The evidence on the value of antibiotics in the milder forms of disease is at present conflicting. In Malaya, FAIRBURN and SEMPLE [20] found that chloramphenicol or penicillin provided no benefit, but soon afterwards MACKAY-DICK and ROBINSON [21] concluded that administration of penicillin begun in the first few days of illness hastened recovery.

In prevention, vaccination has been considered successful in the Italian rice fields,[22] where those at risk are concentrated at the work; but differences of types and more variable exposure have operated against its effectiveness elsewhere. In sugar-cane fields, rice fields, farms, slaughterhouses, fish-gutting sheds, food stores, refuse dumps, sewers, and canals rodents have been destroyed or their access prevented; and leptospires excreted in their urine or in that of domestic animals have been killed by burning or by chemicals. The use of waterproof boots and other protective clothing in piggeries and sewers, and where possible provision of hot water and soap for hand-washing and antiseptic first-aid treatment for cuts and abrasions, have been successful. Prophylactic administration of penicillin after injury has been advocated; but this method failed in a carefully observed case of laboratory infection [23] in which 6 million units of penicillin was given orally during three days, starting one hour after infection.

13. Schneider, M. D. *Exp. Parasit.* 1955, **4**, 107.
14. Schneider, M. D., McLaughlin, J., Jr. *J. Bact.* 1955, **70**, 87.
15. Rothstein, N., Hiatt, C. W. *J. Immunol.* 1956, **77**, 257.
16. Faine, S. *J. Bact.* 1959, **77**, 599.
17. Bull, G. M. *Lancet*, 1955, i, 731, 777.
18. Alston, J. M., Broom, J. C. *Brit. med. J.* 1944, ii, 718.
19. Broom, J. C. *ibid.* 1951, ii, 689.
20. Fairburn, A. C., Semple, S. J. G. *Lancet*, 1956, i, 13.
21. Mackay-Dick, J., Robinson, J. F. *ibid.* 1959, i, 100.
22. Babudieri, B. *Zbl. Bakt.* 1957, **168**, 280.

Myocardial Injury from Therapeutic X Rays

WHEN the myocardium is included within therapeutic X-ray fields, electrocardiographic changes may result. The myocardium may be thus implicated during therapeutic X-radiation of breast cancer and of intrathoracic lesions, such as bronchogenic carcinoma, malignant mediastinal masses, and tumours of the thymus. Critical studies of such cases are complicated by the effects on cardiac function (such as dysrhythmias, or displacement, or mediastino-pericarditis) which these lesions may, of themselves, produce. For critical analysis the best material is provided by cases of breast carcinoma in which X-radiation has been applied: JONES and WEDGWOOD [24] report on 25 such cases and CATTERALL and EVANS [25 26] on 20. The patients were all examined clinically, radiologically, and electrocardiographically before radiotherapy, and at intervals afterwards. No clinical or radiological abnormalities attributable to X-ray therapy were noted in either series, so the discussion centres on the interpretation of electrocardiographic changes.

Of JONES and WEDGWOOD's 25 patients, 21 had electrocardiographic (E.C.G.) changes after radiotherapy, but these workers regarded such changes as pathological in only 4. The particular difficulty is to interpret T-wave changes confined to leads V_1 and V_2—leads which overlie the portion of the heart most exposed to radiation when parasternal fields are used. WHITFIELD and KUNKLER [27] attributed changes in these leads to direct damage to the heart-muscle itself, for the E.C.G. changes corresponded in time with the erythematous skin reactions. JONES and WEDGWOOD regarded the E.C.G. changes in 17 of their 21 patients as non-pathological and due to various causes such as physiological variations in E.C.G. tracings in the same individual, the effects of posture and respiratory movement, and the influence of the operation scar, of skin reactions to X rays, and of breast size. Changes they accepted as pathological consisted in flattening and inversion of T waves in leads V_4 to V_7, which overlie the left ventricle (2 cases), and ST-segment changes (2 cases). These changes are non-specific, and JONES and WEDGWOOD suggest that small areas of pericarditis would account for them. They believe that pre-existing ischæmic heart-disease may have been a factor in all 4 cases, and that the E.C.G. changes, while pathological, were trivial, unaccompanied by symptoms, and usually transient, and " should not be used on present evidence to limit essential radiotherapy ".

CATTERALL's patients were treated by glancing fields of X rays, not by direct parasternal fields, and a method was devised to ascertain the part of the heart actually irradiated and the dose received. By this technique of

23. Broom, J. C., Norris, T. St. M. *Lancet*, 1957, i, 721.
24. Jones, A., Wedgwood, J. *Brit. J. Radiol.* 1960, **33**, 138.
25. Catterall, M. *ibid.* p. 159.
26. Catterall, M., Evans, W. *Brit. Heart J.* 1960, **22**, 168.
27. Whitfield, A. G. W., Kunkler, P. B. *ibid.* 1957, **19**, 53

irradiation, E.C.G. changes were observed only in patients who had the left side of the chest irradiated. Of the 12 such cases, significant E.C.G. changes were found in 9; in the remaining 3 cases marker films had already shown that the myocardium would receive less than 1000r. T-wave changes developed in the 9 patients; these were noted four months after irradiation, persisted at nine months, but had disappeared at twelve months. The changes were attributed to temporary myocardial damage.

CATTERALL made anatomical dissections which show so close a relation between the internal mammary lymph-nodes and the heart that it is difficult to believe that a significant dose of X rays can be given to the former without injuring the latter. Experimental work [28–30] has shown that X-radiation may cause direct injury to the myocardium (evident macroscopically, histologically, and in the electrocardiogram) within days or a few weeks after irradiation. What may be more important is the endarteritis and subsequent vascular occlusion caused by X rays, contributing to the post-radiation syndromes which arise after several months—a latent period evident in radiation nephritis [31 32] and in radiation myelitis.[33–36] Radiation arteritis of the coronary vessels is a distinct possibility: PEARSON,[37] for instance, described extensive myocardial infarction six months after chest irradiation in 2 women under the age of 50, observing that " the attacks were of great severity, accompanied by disturbances of conduction and followed by a degree of clinical and electrocardiographic recovery that one could not expect after atheromatous occlusion".

Two main factors have prevented proper appreciation of the incidental dangers of X-ray therapy—the long latent period between the therapy and important clinical manifestations of such incidental damage, and the understandable concentration of the radiotherapist on the tumour. It has been known for about thirty years that irradiation may damage the heart, but apparently so far no systematic long-term clinical observations on large numbers of patients irradiated in this way have been made. The reports discussed here are useful—though JONES and WEDGWOOD possibly underestimate the problem—but their value is limited by the smallness of the series, bearing in mind that sensitivity to X rays notoriously varies between different people. We agree that the risk of damage to structures other than the malignant tumour may have to be accepted when radiotherapy is the best line of treatment. We must know, however, what such incidental risks amount to. Enthusiasm for, and skill in, a technique of therapy should be associated with unbiased evaluation of the total risks to the patient.

28. Hartman, F. W., Bollinger, A., Doub, H. F., Smith, F. J. *Bull. Johns Hopk. Hosp.* 1927, **41**, 36.
29. Warthim, A. S., Pohle, E. A. *Arch. intern. Med.* 1929, **43**, 15.
30. Hartman, F. W. *ibid.* p. 32.
31. Luxton, R. W. *Quart. J. Med.* 1953, **22**, 215.
32. Wilson, C., Ledingham, J. M., Cohen, M. *Lancet*, 1958, i, 9.
33. Boden, G. *Brit. J. Radiol.* 1948, **21**, 464.
34. Boden, G. *J. Fac. Radiol., Lond.* 1950, **2**, 80.
35. Russell, D. S., Wilson, C. W., Tansley, K. *J. Neurol. Neurosurg. Psychiat.* 1949, **12**, 187.
36. Dynes, J. B., Smedal, M. I. *Amer. J. Rœntgenol.* 1960, **83**, 78.
37. Pearson, H. E. S. *Lancet*, 1958, i, 222.

Annotations

GENIUS AND CULTURAL PROGRESS

STUDENTS of society, present and past, have often asked themselves what are the agents that determine the rapid, almost miraculous, advance shown by certain cultures at different times. Offering some views on this crucial topic in his Hobhouse lecture at University College on May 30, Sir Aubrey Lewis, professor of psychiatry in the University of London, pointed to the inherent stability and conservatism of societies, which, he said, incorporated ideas of radical change only under conditions of dire threat. " Progress " he thought was hard to assess; for while, in general, material, æsthetic, and social values ran parallel, this was not always so: for example, present material achievements were enormous, but they had scarcely been equalled in the æsthetic and moral spheres. Environmental pressures—from climate, contact with other societies, and so on—were undeniable; but their extreme forms (e.g., upon the Eskimos) were uncommon and could not account for the most dramatic advances. Though, historically, some logical order could be seen—for instance, in scientific discovery—it was impossible to tell why a certain triumph was achieved by a given man at a given time. The sociologist Robert Merton, in his careful study, had attributed the 17th-century rise of science to the " Calvinist spirit " of the puritans—a spiritually derived flow of practical activity, by those believing themselves specially chosen of God, which later became secularised (some discoveries actually antagonising the theologians). But different cultures undoubtedly provided different circumstances for such flowering. Bitter denial of legitimate progress, such as we still see in the field of art, was no longer a danger in science; and over-credulity, if anything, was more probable. Scepticism Sir Aubrey did not regard as a harmful commodity; indeed if it had been more in evidence latterly humanity would have been saved enormous suffering. Minds, it had been said, tended to fall into a critical-destructive or creative-accepting group; the merits and demerits of these antitheses were not easy to judge.

The concept of the " great man " in this context had been disparaged but it undoubtedly contained much truth. Such exceptional individuals—e.g., in science—were usually outstanding personalities in their own right; the apex being reached, Sir Aubrey thought, by men like Darwin, Galileo, and Newton. Great men were, in large measure, obviously products of their society. Much dispute had surrounded the alleged characteristics of such people, and criticism of them often arose from the injured narcissism of lesser mortals, who raised their own self-esteem by pulling the mighty from their pedestals: such could not fail to impede advance. Genius had been described as " a transcendent capacity for taking trouble ", but there was much to be said for Samuel Butler's suggestion that it was an infinite capacity for getting into trouble! In particular, Sir Aubrey differed from the views of Kretschmer and others equating genius with insanity: the idea that a psychopathic element was essential he believed to be erroneous, though comforting to some. Genius and mental disease might coexist, though probably no more commonly than might be randomly expected, and the affliction was often limited to old age. Early schizophrenia, mania, or toxic psychoses might provide the exceptional mind with flashes of intuition and release of inhibition, though essentially the schizo-

phrenic process caused impoverishment and decay. Depression—" the dark night of the soul "—could add artistic depth; but the disturbed mind could not meet the demands of science, nor could mental illness beget great works and bring them to fruition. Intelligence played an important part; but beyond a certain level less quantifiable personality factors were crucial elements in success—stability, satisfactory marriage, and so forth—and with personality distortions a high intelligence quotient was, indeed, dangerous. But, geniuses apart, all scientific achievement depended on careful dedicated research by numbers of more " ordinary " people.

In conclusion, Sir Aubrey criticised our current preoccupation with abnormal and subnormal aspects of personality and suggested that psychologists, sociologists, and psychoanalysts should look more at the positive features of human beings, and at the possible ways these attributes may be nurtured. The potential powers of the human mind, as shown particularly in infant prodigies, were almost inconceivably vast, and such study might help to guide and hasten cultural advance.

UNIVERSITY PLAN FOR NEWCASTLE

A SPECIAL convocation of the University of Durham will next week consider the separation of the Durham and Newcastle divisions of the university and the establishment of an independent university in Newcastle. This step has the support of the governing bodies of both divisions.

The University of Durham was founded in 1832. Two years later, and quite independently, the " Newcastle upon Tyne School of Medicine and Surgery " was established. In 1852 the school became associated with the university, and from 1870 it was known as the " University of Durham College of Medicine ". In 1871 the " University of Durham College of Physical Science " opened in Newcastle—its name being changed to Armstrong College in 1904. Finally, the College of Medicine and Armstrong College were united in 1937 as King's College, which constitutes the Newcastle division of the University of Durham.

With the growth and development of both divisions the question of separation has long been under discussion. About ten years ago a proposal to change the name of the University to " University of Durham and Newcastle " was defeated by graduates in convocation—probably wisely, since it would have done little to solve the problems inherent in running a federal university whose divisions are fifteen miles apart. The difficulties are by no means only administrative but involve the academic control of curricula and examinations. Now Durham has 1600 students and Newcastle 3600, and they have been asked to prepare respectively for 3000 and 6000 by 1970.

Several, but not all, of the major faculties are now represented in each division. Medicine, as well as some others, is pursued only in Newcastle. Here also is a large dental school. Separation, if it comes, will be regretted by a large number of graduates, especially in medicine. Probably the great majority of these cherish the association of their school with the ancient city and cathedral of Durham, and they believe also that the prestige of Durham medical degrees is something not readily replaced. Full appreciation of the wider issues involved may not be easy. We can safely say, however, that those who regret the prospect of separation, and many who approve it, would be even more disturbed if the new university were given any other name than that of the city of Newcastle in which it has grown from small beginnings to one of the largest provincial university institutions.

CONTINUING SECULAR TREND IN GROWTH

IT is now well established that there has been a continuous trend toward earlier maturation in children in Western Europe and America during the past hundred years: the age of menarche has been getting earlier by approximately 4 months per decade, at least during the present century.[1] This trend shows no signs as yet of abating.[1] The two latest items of information are from schools in Sussex and from the London County Council. In 1950 Wilson and Sutherland [2] reported a mean age of menarche of 13·38 years for a sample of children attending Dorset day-schools; and now, nearly ten years later, they report a figure of 13·03 years for children attending Sussex day-schools.[3] Since the circumstances of these two samples are believed not to differ it seems that the difference between these figures is attributable to the secular trend, which works out at very close to the figure of 4 months per decade. The recent survey carried out by the London County Council will, we understand, show a very similar trend in comparison with the figures of 5 years ago. The average age of menarche in this country, at least in the south, is evidently now just about 13·0 years. Clearly the trend may be expected to stop soon, but there is still no evidence of its doing so. The importance of future periodic surveys should be obvious both to medical and to educational authorities.

A FRUITFUL CENTURY

THE National Hospital for the Paralysed and Epileptic received its first patients, at 24, Queen Square, Bloomsbury, in June, 1860; and next week it will celebrate its centenary.

It was founded through the efforts of Miss Johanna Chandler, aided by her sister Louisa, and the good will of Alderman David Wire, lord mayor of London in 1859, and himself a sufferer from a chronic nervous disease. At a Mansion House dinner in November, 1859, a society was formed for the purpose of establishing and maintaining a hospital, and a board of management was set up with David Wire as chairman. Two physicians were later appointed in preparation for the opening—J. S. Ramskill, assistant physician to the London Hospital, and C. E. Brown-Séquard, who, with an international reputation already established, had now decided to set up in practice in London. The hospital rapidly became popular, and another physician and surgeon were appointed in 1860. In 1862 a young man named Hughlings Jackson, destined to become the greatest figure in British neurology, was appointed assistant physician, with the additional duty of visiting patients in their homes. When Brown-Séquard resigned on leaving London in 1863, another physician was appointed, Jackson being passed over at that time. In the next ten years, those joining the staff included a group from University College Hospital—Russell Reynolds, H. C. Bastian, and William Gowers—all three of whom, as well as Jackson, later became fellows of the Royal Society. Within a few years the hospital had acquired the adjoining

1. Tanner, J. M. Growth at Adolescence. Oxford, 1955.
2. Wilson, D. C., Sutherland, I. *Brit. med. J.* 1950, ii, 862.
3. Wilson, D. C., Sutherland, I. *J. Obstet. Gynæc. Brit. Emp.* 1960, **67**, 320.

houses, and it has gradually extended until now it occupies more than half the east side of Queen Square, with activities overflowing into adjacent buildings.

From the beginning, the hospital had a high academic standing, and Brown-Séquard's weekly lectures were the start of the present Institute of Neurology. Although some outstanding experimentalists, such as Brown-Séquard, David Ferrier, and Victor Horsley, were members of its honorary staff, the fame of the National Hospital, like that of Charcot and his school in France, was founded on clinical neurology. Ferrier's experimental observations on the localisation of function in the brain were the complement of the clinicopathological observations of Jackson, which were based particularly on the study of partial convulsions and those beginning unilaterally. Jackson's chief legacy, however, is not clinical observations but a philosophy of neurology: he was always looking for the general laws behind the individual phenomena. "In this regard," as Sir Gordon Holmes has said, "his hypotheses of evolution and dissolution of function and of release of function, his conception of the unit of referential speech as the proposition and not simply the word, stand out as amongst his greatest contributions." Clinical study led to the differentiation of diseases and syndromes, and these were magnificently described in William Gowers' *Manual of Diseases of the Nervous System*. This was based on his own observations, and his descriptions of disease were masterly.

To the next generation of Queen Square physicians belong the classical description of subacute combined degeneration of the cord by Risien Russell, F. E. Batten, and James Collier (following earlier observations by James Taylor), Holmes'—also classical—work on the symptoms of cerebellar disorders and on the cortical representation of vision, and Kinnier Wilson's account of progressive lenticular degeneration. J. G. Greenfield, as the first whole-time pathologist, reaped a rich harvest, and has a number of first descriptions to his credit. In 1893, Gowers had written that "idiopathic cerebritis" was almost unknown, and this state of affairs persisted till the epidemic of encephalitis lethargica during and after 1919. Greenfield studied its pathology with Farquhar Buzzard, and then investigations of other forms of encephalitis came thick and fast—those following vaccination and measles; other forms of demyelinating encephalitis; the encephalitis periaxialis of Schilder (whose clinical recognition is due to Collier) and its different types; and then the leucoencephalitis of children and the varieties of inclusion-body encephalitis. In fact, except for cerebral abscess and syphilis, our knowledge of inflammation of the brain has all been gained within a generation.

Outpatient teaching was developed at an early stage, particularly by Gowers, but nowadays teaching occupies a far bigger place than ever before. The former medical school has become the Institute of Neurology, part of the University of London. Also the hospital houses two research units set up by the Medical Research Council. But though "The National" has in this way gone far beyond the purposes of its founders, it preserves, explicitly as well as implicitly, part of its original charitable foundation. When the hospital was taken over by the National Health Service, the society which formerly ran it remained in being. In 1902 it had received a royal charter, and as the "Chartered Society" it not only acts as the "friends of the hospital" but also carries on the second of the forms of social service established by Johanna Chandler—namely, a pension fund for paralysed patients. The number of pensions is now about a hundred; and though they are small they help to meet the special needs of paralysed patients. Sir Ernest Gowers has been chairman of this society for many years.

BACKED BY THE COMMUNITY

LIKE many other admirable institutions which have been started by private good will, our system of university awards and scholarships has been taken over and developed by the community as a form of enlightened self-interest. A modern State which needs a great many highly educated citizens must ensure that enough suitable young people have an opportunity to attend a university. Already over 80% of our students hold awards from public funds. In 1951–52 the cost of these university awards was £5·6 million; in 1958–59 it was £21·6 million. The need for graduates continues to grow steadily, and two years ago the Minister of Education and the Secretary of State for Scotland appointed a committee, under the chairmanship of Sir Colin Anderson, to consider the present system of university grants. The committee, which has now reported,[1] besides suggesting many useful modifications of detail, have recommended two major changes.

The first, which has the support of the whole committee, is that any student (ordinarily resident in Great Britain) who is accepted by a university and who has attained a minimum entry qualification (2 G.C.E. passes at A level in England and Wales) should automatically qualify for an award. This would in effect shift the responsibility for selection from the local authorities to the universities, abolish one academic hurdle, and offer equal facilities to students from every part of the country. Public funds cannot be used to finance the "perpetual student", and awards would ordinarily be given only for first degree courses. But the committee recommend that the claims of students who for some good reason wish to take a further course should be considered sympathetically. As a deserving exception of this kind they specially mention "exceptionally able medical students who are recommended to interrupt their medical courses in order to undertake a specialist course in a related scientific subject, such as bio-chemistry".

The second important change which the report discusses is the controversial issue of parental contributions to awards. Here the committee were themselves divided. Eleven members recommended that parental contributions should be abolished; five members would like to see them retained at any rate for the present, though in a modified form. All were agreed that some young people lose the chance of a university education because the present system falls hardly on their parents. The "abolitionists" in presenting their case make the further point that by the new "family pattern" many young people who take jobs became financially independent of their parents in their teens. Should not the student, who must work at least as hard as his wage-earning contemporaries, also be given a measure of independence? The committee also draw attention to the growing number of scholarships offered without regard to parental income by industrial bodies and nationalised boards and ask whether these may not deflect an undue proportion of students into certain careers, leaving others, such as medicine, with less than their proper share. Under the present system the

1. Grants to Students. Cmnd. 1051. H.M. Stationery Office. 1960. Pp. 136. 6*s*. 6*d*.

long training required by medicine and dentistry is a further disincentive to recruitment to these professions.

The case of the anti-abolitionists deserves respectful consideration. A university education cannot, and should not, be offered to every citizen; should not then those who are able be asked to contribute to what is in effect a selective service? Are not parental contributions safeguards of self-reliance and self-respect for the citizen and of a small State-free income for the universities? Cannot too much importance be given to university education? May not some clever students lost to the university do the nation more good by climbing some other ladder? But even the minority group would like to see the parental contribution modified. The amendments proposed would have the effect of reducing the present total parental contribution from nearly £5 million to £2 million. And this reduction strengthens the case for abolition. To be fair a system of contributions must be complex, and in practice administrative expense and effort might well become disproportionate to such a vestigeal remainder. Furthermore the majority recommendation for the abolition of parental contributions proposes that parents should no longer be eligible for income-tax or surtax child allowances for students receiving awards. With this proviso the committee estimate that the discontinuance of parental contributions would only cost the tax-payer an extra £1 million.

Sir David Eccles has announced that the Government are to discuss the report as soon as possible with universities, local authorities, and schools, but he warned the House of Commons that even so the earliest date by which any new arrangement could be introduced would be 1961.

DRUG-RESISTANT STAPHYLOCOCCI IN THE FARMYARD

SEVEN years ago regulations were made under the Therapeutic Substances (Prevention of Misuse) Act permitting the addition of penicillin and chlortetracycline to the diet of pigs and poultry. The accelerated growth-rate of animals fed on diets containing antibiotics is well known (although the mechanism remains uncertain), and the economic advantages have led to the widespread addition of antibiotics—particularly tetracycline. The wisdom of this procedure, in view of the possible development of drug-resistant infections in the animals, has been questioned; but, as we pointed out last year,[1] so far no disastrous results have followed.

As was anticipated, changes in the bacterial flora of the intestinal tract have included not only a reduction in the numbers of certain species, notably *Clostridium welchii*,[2] but also the emergence of drug-resistant strains of *Escherichia coli*,[3] *Cl. welchii*,[4] and probably other intestinal bacteria. These findings have been largely disregarded, and indeed outbreaks of infection due to drug-resistant intestinal bacteria have not occurred.

An unexpected and somewhat disturbing discovery, reported by Smith and Crabb,[5] is that pigs and chickens fed on antibiotics and also their attendants may become carriers of drug-resistant staphylococci.

These workers compared the nasal and skin staphylococci of 160 pigs from sixteen herds which had been fed for one and a half to three months on a diet containing 10–20 g. chlortetracycline or oxytetracycline per ton, with those of a control group of 160 pigs from sixteen herds not fed on antibiotics. Of the tetracycline-fed animals 72% carried *Staph. aureus* and 67% carried tetracycline-resistant strains. In the control group the total carriage-rate was lower (57%) and tetracycline-resistant strains were isolated from only 4%. None of the strains isolated from either group was penicillin-resistant. In a third, smaller, group of 38 pigs from four herds fed on diets containing penicillin 87% of the animals carried *Staph. aureus* and 37% carried penicillin-resistant strains.

Similar studies were made on 100 chickens from ten flocks that had been maintained for ten to eleven weeks on a diet containing 5 g. procaine penicillin G per ton and 10–15 g. chlortetracycline per ton; these were compared with a control group of 100 chickens from ten flocks not fed on antibiotics. In the antibiotic-fed group 95% carried *Staph. aureus*, and of a total of 492 strains isolated 41% were penicillin-resistant and 19% penicillin- and tetracycline-resistant. In the control group a smaller proportion—58%—carried *Staph. aureus* and of 246 strains isolated 3% were penicillin-resistant, 3% tetracycline-resistant, and 1% penicillin- and tetracycline-resistant.

Finally the staphylococcal carriage of the attendants was studied. Of 37 men looking after pigs not fed on antibiotics 35% carried *Staph. aureus*; 5% carried penicillin-resistant strains, but none carried tetracycline-resistant staphylococci. Of 35 men looking after tetracycline-fed pigs 57% carried *Staph. aureus*; 11% carried penicillin-resistant strains; 34% carried tetracycline-resistant strains; and 3% carried strains resistant to both antibiotics. In a third group of 50 attendants of tetracycline- and penicillin-fed chickens the carriage-rates were: total *Staph. aureus* 48%, penicillin-resistant 30%, tetracycline-resistant 14%, penicillin- and tetracycline-resistant 4%.

Study of the bacteriophage types of the tetracycline-resistant staphylococci showed that one type was predominant in each herd or flock and that, with the possible exception of one flock, staphylococci from the attendants belonged to the same phage type as those from the pigs and chickens.

Thus, as in hospitals, both cross-infection and antibiotic administration appear to have played a part in the increased prevalence of drug-resistant staphylococci. At least in the attendants the presence of antibiotic in the environment seems likely to have been a factor. (Two years ago Gould[6] reported that this was an important cause of nasal colonisation of hospital staff with penicillin-resistant *Staph. aureus*.) Smith and Crabb suggest that the higher prevalence of tetracycline-resistant strains in pigs and their attendants may have been related to the fact that the pigs were fed on dry meal, which would more readily yield antibiotic-laden dust than the pelleted food used for chickens. The analogy between hospital and farmyard is of considerable interest; but it cannot be assumed—and is perhaps unlikely—that the situation in the farmyard is potentially so dangerous.

Nevertheless, whatever the danger for animals, a further source of drug-resistant staphylococci in man must give us pause; and a study by McDonald et al.[7] suggests that the use of antibiotics in animal diets may have wider implications. These investigators found a higher nasal carriage-rate of penicillin-resistant staphylococci in R.A.F. recruits coming from rural areas than in those coming from towns. They suggested that this might

1. *Lancet*, 1959, i, 402.
2. Lev, M., Briggs, C. A. E., Coates, M. E. *Nature, Lond.* 1956, **178**, 1125.
3. Smith, H. W., Crabb, W. E. *Vet. Rec.* 1957, **69**, 24.
4. Smith H. W. *J. Path. Bact.* 1959, **77**, 79.
5. Smith, H. W., Crabb, W. E. *ibid.* 1960, **79**, 243.
6. Gould, J. C. *Lancet*, 1958, i, 489.
7. McDonald, J. C., Miller, D. L., Jevons, P. Williams, R. E. O. *Proc. R. Soc. Med.* 1960, **53**, 255.

be associated with the drinking of unpasteurised milk from penicillin-fed cows, which may contain penicillin-resistant staphylococci [8] and small quantities of penicillin.[9] A further explanation is that most people in rural areas have connections with farms, and that the recruits might, therefore, have had direct contact with penicillin-fed animals or their attendants. It is noteworthy, however, that less than 0·5% of the recruits carried staphylococci resistant to tetracycline,[10] which was the commonest form of resistance recorded by Smith and Crabb.

THE CHESHIRE HOMES

"WHAT can't be cured must be endured" is a harsh but realistic saw, and, as our Disabilities series proved, people show almost unbelievable courage and resource in coming to terms with their handicaps and learning how to live with them. The task is hardest for those who, despite all the help that improved methods of reablement can give, have to face a future in which they will always need some form of institutional care. At present many of them are looked after in hospitals, where, even in a friendly ward, life must conform to a fairly rigid discipline that must fall heavily on the "resident" patient. In his presidential address to the section of physical medicine of the Royal Society of Medicine on June 8, Dr. Basil Kiernander reviewed sympathetically the needs of this group of patients and modern methods of helping them. He described in particular the work of the Cheshire Homes for the Chronic Disabled, which from the smallest beginning have spread all through the United Kingdom and overseas. There are now 16 homes in this country, with 8 more planned, 7 in India, 2 in Malaya, 2 in Poland, and 1 each in Nigeria, the Lebanon, and Jordan. The first international home, called Raphael, has been started at Dehra Dun at the foot of the Himalayas and is to be expanded as a training centre and example of the ideal home.

The Cheshire Homes vary according to local needs and local opportunities: some are converted old mansions, while some are modern houses built with the advice of the patients. But all encourage their disabled residents to lead a useful life and to help each other. Often the patients have to retrain themselves in the simple activities of daily living: as a patient put it, "all the little things that make you miserable when you cannot do them, like putting on your shoes, taking your soup, switching on the light". In the new home soon to be opened at Dulwich Dr. Frank Cooksey and his colleagues are providing gadgets for a specially laid out kitchen.

The experience of the twelve years since the first home was started by the Cheshire Foundation has suggested some general principles:

About three-quarters of the patients in a home should need little nursing. Not more than a quarter should be incapacitated by age or dying. About 40 patients seems to be the best number. With fewer, the home is an uneconomic proposition; with more, the atmosphere easily becomes institutional. A preponderance of patients with any special disorder is unwise. For instance, if more than half of the patients in a house have disseminated sclerosis there are temperamental difficulties. It is unwise to mix the young and the elderly. Some specialised homes have, however, been opened. In India, for instance, there is need for homes for leprosy patients at different stages of the disease. There is one home for mentally defective children in this country and another in India. There is one home where patients who have left a mental hospital spend a few months before returning to their own homes.

Each home is run by a small committee. The members are local people and links with the outside world. They invite the patients to their homes and make contacts with local industry. The committee are responsible for the financial administration of the home and for the selection of patients for admission. There is a matron or warden in charge of the home; but the patients share in the daily work of the home, helping with laundry, cooking, washing up, and looking after each other. A welfare committee drawn from the patients run the funds, canteens, newspapers, and entertainments. They are also encouraged to take up dressmaking, painting, manufacturing handicrafts, and printing as serious occupation. The proceeds of the sales go to the welfare fund. The running cost of the homes with the help of patients and volunteers has been kept as low as £6–7 a week per bed. In each home two or three beds are reserved for disabled visitors who come while their families are on holiday or from other Cheshire Homes for a change.

Dr. Kiernander suggested that the hospital service might with profit study this independent experiment in helping the disabled to lead "not just an existence but a happy and useful life."

BIRTHDAY HONOURS

AMONG the new honours, we are glad to welcome first the name of Dr. A. M. W. Rae, chief medical officer of the Colonial Office, whose K.C.M.G. recognises devoted service beginning in West Africa in 1924. Air Vice-Marshal Rumball, who is promoted K.B.E., has not allowed his many other qualifications to diminish his distinction as a physician, and is a treasurer of the Royal Society of Medicine. Of the new knights bachelor, Dr. Robert Aitken left the regius chair of medicine at Aberdeen in 1948 to become vice-chancellor successively at Dunedin and Birmingham. His chairmanship of the Committee of Vice-chancellors and of the Overseas Research Council bears witness to qualities long familiar to his medical friends. Dr. W. E. Chiesman has continued the tradition of wisdom and independence evident in Medical Advisers to the Treasury, and is president of the Association of Industrial Medical Officers. Dr. John Richardson, physician to St. Thomas's Hospital, consulting physician to the Metropolitan Police, and editor of an interesting textbook, is a man whom his colleagues are always glad to consult. Mr. B. W. Rycroft, amid much ophthalmological achievement, has become one of the pioneers whose names are remembered; for many in years to come will owe their sight to his unceasing effort to make corneal grafting a generally practicable operation. The knighthood bestowed on Mr. Douglas Robb comes happily at the beginning of his visit to Britain as Sims professor of surgery. Thoracic surgeon, pro-chancellor of the University of Auckland, and president-elect of the British Medical Association, he is notable also, and especially, as a person. Also in Australasia, Lady Herring is created D.B.E. for her welfare work particularly in nursing organisations in Victoria, where her husband is Lieutenant-Governor.

The list appearing on p. 1342 contains many other names which are already honourably familiar in the profession.

Dr. ALEXANDER KENNEDY, professor of psychological medicine in the University of Edinburgh, died on June 11 at the age of 51.

8. Tee, G. H. *Mon. Bull. Minist. Hlth Lab. Serv.* 1957, **16**, 141.
9. Panes, J. J., Edge, M., Hobson, M., Thomas, S. B. *J. Soc. Dairy Tech.* 1957, **10**, 81.
10. Williams, R. E. O. Personal communication.

Public Health

A POLIOMYELITIS EPIDEMIC IN GREECE

GUNNAR GILLE
M.D.
DEPUTY HEAD OF THE HOSPITAL FOR CONTAGIOUS DISEASES, STOCKHOLM, SWEDEN

BEFORE 1949 only sporadic cases of poliomyelitis were encountered in Greece, and these were practically never in the acute stage, though the sequelæ—i.e., flaccid paralyses—were occasionally seen in children. The prevalence of paralytic cases since 1949 is shown in fig. 1.

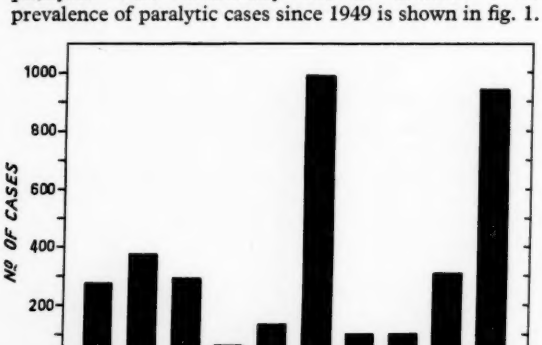

Fig. 1—Prevalence of paralytic poliomyelitis in Greece, 1949-58.

In the past 10 years there have been usually not less than 100 cases of paralytic poliomyelitis a year. In 1954 the paralytic cases numbered about 1000, and these were chiefly in the northern regions. Most of the patients were less than three years old, and the mortality-rate was below 4%.

The Epidemic

A serious outbreak of poliomyelitis began in May and June, 1958. In June some 200 patients were treated at the children's clinic in Athens, and the mortality in this group was 20%. The Greek Red Cross appealed for help from the International Red Cross League, and I was sent to Greece as delegate of the Swedish Red Cross to report on the situation and to assess the help required.

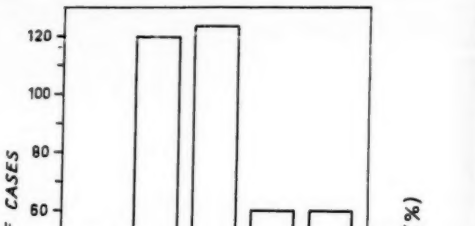

Fig. 3—Cases of paralytic poliomyelitis treated in Athens hospitals and the fatalities, from May to September, 1958.
The respiratory unit started work at the beginning of July.

The children's clinic in Athens was faced with enormous problems through lack of equipment and trained staff—and especially those with knowledge of respiratory treatment. Suction of the airways, systematic turning of the patient, and postural drainage were not practised. Consequently many patients got pulmonary complications.

The immediate need was clearly of a department in which the primary treatment would be to keep the airways free and to standardise the electrolytic and caloric intake. A respiratory department requires, above all, trained staff, and it also needs technical equipment. Both were promptly sent by the Swedish Red Cross. Two poliomyelitis nurses arrived, followed by a physiotherapist, from the Stockholm hospital for infectious diseases. Various respirators, suction pumps, and other equipment were given. The German Red Cross sent two Dräger tank respirators.

A respiratory department, the first in Greece, was established at St. Barbara's Hospital in Athens (the hospital for infectious diseases). Fresh cases of poliomyelitis were admitted to this department from the surrounding area and from remote parts of the country. But the technical resources at St. Barbara's were very limited, and only emergency action could be taken. I was therefore unable to make a clinical classification of the patients.

As soon as the respiratory department was established it was filled with patients, and from July until January, 1959, some 500 cases of poliomyelitis, all paralytic, were treated. Practically no non-paralytic cases were seen. A questionnaire was sent to doctors in the province of Argolis in the Peloponnesos, one of the most severely affected areas, but none reported widespread outbreaks of headache or fever. Many people must have considered these

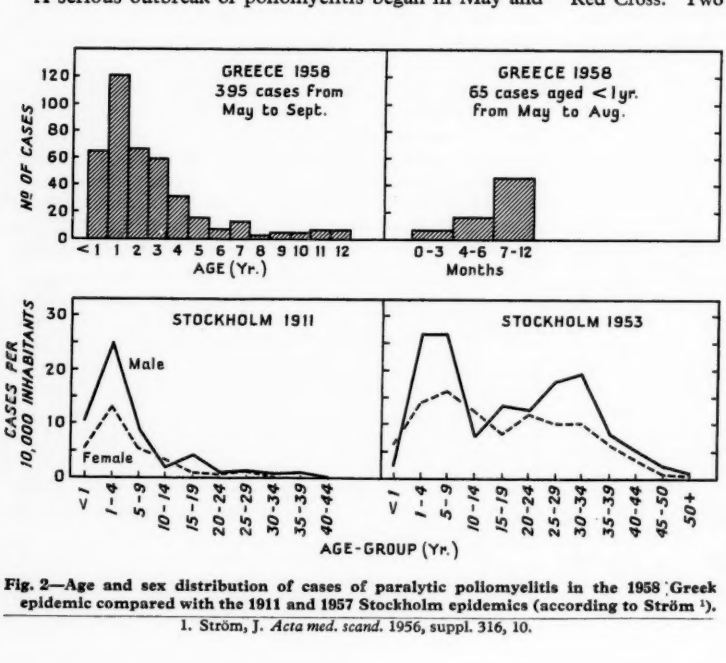

Fig. 2—Age and sex distribution of cases of paralytic poliomyelitis in the 1958 Greek epidemic compared with the 1911 and 1957 Stockholm epidemics (according to Ström [1]).

1. Ström, J. *Acta med. scand.* 1956, suppl. 316, 10.

symptoms too slight to warrant a visit to a doctor. And doctors, when consulted, did not suspect poliomyelitis, because the non-paralytic form is unknown in Greece. Lumbar punctures were not usually performed, although a few were made on suspected non-paralytic cases, all of which proved to be positive. The non-paralytic form naturally occurs though the diagnosis is more difficult in infants than in older children and adults.

Fig. 2 shows the age-distribution of the paralytic cases compared with that in the outbreaks in Stockholm in 1911 and 1953. There were also 4 adult patients, 2 of whom were tourists from Sweden and West Germany. Severe bulbar poliomyelitis has never been seen in Sweden among children under two years of age. But in the Greek epidemic, in which nearly all patients were infants, a few did contract the severe bulbar form, and among these several died. Probably most of them had such severe lesions in the central ganglia that recovery was impossible, yet a few would probably have survived had the conditions been more favourable. Fig. 3 shows the total number of cases, and the mortality-rate month by month.

The overall mortality-rate among 500 patients was 5%, but this figure represents some selection since mild cases were treated elsewhere. In its usual way, the illness increased rather than decreased in severity during the course of the epidemic. Rather more than half the patients required some form of respiratory treatment for various periods. Fortunately respiratory insufficiency and dysphagia were overcome by simple means such as suction, postural drainage, and body respirators.

The Swedish Red Cross assistance lasted from the end of June to October, 1958. The number of new cases gradually diminished until February, 1959, after which no further cases were reported.

Fig. 4—Geographical distribution of cases of paralytic poliomyelitis.

Discussion

The Greek poliomyelitis epidemic in 1958 prompts reflections on the state of immunity in the country. The age-distribution and the relatively few cases—about 1000 paralytic cases in an overcrowded area with 8 million people—suggest that the immunity is generally satisfactory. Since the epidemic it should, of course, have improved. Moreover, geographically practically no part of the country was spared, the patients coming from all provinces and island groups (fig. 4 shows the number of paralytic cases from different parts of the country).

Under the circumstances mass vaccination seemed pointless. If, by virological methods, it were possible to discover any groups of people who were not immune, they should be vaccinated. But this seemed improbable in view of the regular communications between different areas. Within a few years' time the infants may again be exposed to infection. If the virus is present in large amounts under conditions which favour its spread, the intervals between epidemics might be shorter than is usual in the Scandinavian countries. Fig. 1 might suggest a free interval of four years. If that is correct, it would be advisable to vaccinate the youngest children within a year or two. The living, attenuated virus method, which seems to be "around the corner" would be best for this purpose. A single dose by mouth must be the ideal method of mass vaccination in a country such as Greece.

Another threatened group of individuals is tourists from countries with a low immunity. They should be vaccinated beforehand. Non-vaccinated tourists should be given γ-globulin.

With regard to social distribution, though I cannot prove it by statistics, the youngest patients undoubtedly were predominantly very poor. The few older patients came mostly from higher social groups.

I am indebted to the Swedish National Association Against Poliomyelitis for financial aid.

Outbreak of Syphilis

AN outbreak of syphilis in Maryland has been described by Bird and Cornish.[1]

In June, 1959, primary syphilis was diagnosed in a 29-year-old man. Intensive investigation of his contacts and associates, involving examination and blood-testing of over 300 persons, led to the detection of 44 previously unknown cases of syphilis; 28 of these had primary or secondary syphilis, 14 had early latent syphilis, and 2 had late latent syphilis. 31 of the cases were found in three counties on the Eastern shore of Maryland, 7 in four other Maryland counties, and 6 in Delaware and Florida.

26 of the 28 found to have primary or secondary syphilis who were living in Maryland were interviewed and named a further 124 contacts, 47 of whom were found to have syphilis; 23 had had no treatment, and 15 of these had acquired the disease recently and were in the primary or secondary stage. 12 of the 14 with early latent syphilis named 56 more contacts. 16, of whom 5 were not already under treatment, had syphilis; 2 of the 5 had primary or secondary syphilis and 3 early latent syphilis.

Most of the original 44 were from the lower socioeconomic strata; few were regular school attenders or had permanent employment. All but 4 were under 25 years of age, and 25 were under 20, a girl of 13 being the youngest. The oldest patient was 37. All were non-whites; an admitted prostitute named several white men as contacts, but none of them was infected. Those involved were promiscuous, one 17-year-old girl, for example, having had intercourse with 22 different men in six months.

A case-finding method called "cluster testing" was used, involving investigation not only of sex contacts of patients, but also of friends and associates who might have been exposed—including,

1. Bird, C. D., Cornish, T. L. *Maryland Dep. Hlth mon. Bull.* 1960, **32**, no. 2.

for example, the patrons of a bar frequented by many of those involved.

This outbreak occurred in a stable and progressive community with good medical and public-health facilities. It points to the continuing need for an active control programme even in areas assumed to have a low prevalence of syphilis.

Food Additives in America

In the United States the cherished principle that the accused is innocent till proved guilty no longer applies to food additives. Hitherto the Food and Drug Administration have had to prove a material dangerous before banning it; but since March there has been a ban on any material not authorised. The Administration published a list of 453 such substances " generally regarded as safe "; in other cases the manufacturer must ask the Administration for specific clearance or must file a petition (with evidence that the substance is harmless) for regulations prescribing its use. This shift in the burden of proof involved the food industry in a great deal of work in obtaining the required evidence, and many firms asked for grace.[1]

1. *Christian Science Monitor*, Feb. 25, 1960.

Infectious Diseases in England and Wales

Disease	Week ended May			
	7	14	21	28*
Diphtheria	2	1	2	2
Dysentery	1096	1038	1151	1312
Encephalitis:				
Infective	..	..	4	4
Postinfectious	4	2	1	1
Food-poisoning	121	156	151	157
Measles, excluding rubella	1575	1752	1886	2254
Meningococcal infection	14	15	20	25
Ophthalmia neonatorum	31	24	21	21
Paratyphoid fever	4	2	12	3
Pneumonia, primary or influenzal	292	290	250	256
Poliomyelitis:				
Paralytic	7	1	2	6
Non-paralytic	3	2	5	6
Puerperal pyrexia	143	178	209	196
Scarlet fever	533	593	624	606
Smallpox	..	..	..	..
Tuberculosis:				
Respiratory	416	457	464	459
Meninges and C.N.S.	4	9	3	8
Other	52	53	64	61
Typhoid fever	1	2	1	3
Whooping-cough	1201	1362	1458	1453

* Not including late returns.

Special Articles

BIRTHDAY HONOURS

THE list of honours published on June 11 contains the names of the following members of the medical profession:

K.C.M.G.

ALEXANDER MONTGOMERY WILSON RAE, C.M.G., M.D. Edin.
Medical adviser to the Secretary of State for the Colonies.

K.B.E. (Military)

Air Vice-Marshal CAMPION AUBREY RUMBALL, C.B.E., F.R.C.P., Q.H.P.

D.B.E.

MARY, Lady HERRING, M.B. Melb.
For social welfare services, especially with the nursing organisations of Victoria.

Knights Bachelor

ROBERT STEVENSON AITKEN, M.D. N.Z., LL.D., D.SC., F.R.C.P.
Vice-Chancellor, University of Birmingham.

WALTER ERIC CHIESMAN, C.B., M.D. Cantab., F.R.C.P.
Medical Adviser, H.M. Treasury.

JOHN SAMUEL RICHARDSON, M.V.O., M.D. Cantab., F.R.C.P.
Physician, St. Thomas's Hospital, London.

GEORGE DOUGLAS ROBB, C.M.G., M.D., CH.M., B.SC., N.Z., F.R.C.S., F.R.A.C.S.
Consulting surgeon, Greenlane Hospital, Auckland, New Zealand.

BENJAMIN WILLIAM RYCROFT, O.B.E., M.B. St. And., F.R.C.S.
Ophthalmic surgeon, Queen Victoria Hospital, East Grinstead.

C.B. (Military)

Major-General GILBERT THOMAS LANCELOT ARCHER, M.B. Dubl., F.R.C.P.I., Q.H.S.

Major-General WILLIAM DILLON HUGHES, C.B.E., M.D. Belf., F.R.C.P.I., Q.H.P.

Surgeon Vice-Admiral WILLIAM ROBERT SILVESTER PANCKRIDGE, M.R.C.S., Q.H.P.

Surgeon Rear-Admiral DERMOT FRANCIS WALSH, O.B.E., M.B. Dubl., F.R.C.S.E., Q.H.S.

C.B.E. (Military)

Brigadier LESLIE REGINALD HEBER KEATINGE, O.B.E., M.B. Dubl., late R.A.M.C.

Air Commodore GERARD WARD MCALEER, M.B. N.U.I., Q.H.P., R.A.F.

Colonel JOHN GEORGE GLYNN WHITE, O.B.E., E.D., M.B. Melb., R.A.A.M.C.

C.B.E. (Civil)

DAVID BROWN, M.B. Lpool.
For political and public services in Bootle.

LAWRENCE JOHN CLAPHAM, M.D. Lond.
Director of medical services, North Borneo.

JAMES GRAHAM, M.A., M.B. Edin.
Senior administrative medical officer, North East Metropolitan Regional Hospital Board.

IAN DINGWALL GRANT, M.B. Glasg., Hon. M.D. Birm.
Lately president, College of General Practitioners.

LUDWIG GUTTMAN, O.B.E., M.D. Freiburg, M.R.C.P.
Director, National Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury.

HENRY MCLORINAN, M.B. Melb., F.R.A.C.P.
Medical superintendent, Fairfield Hospital, Victoria.

MARTIN AMSLER RUSHTON, M.D. Cantab., F.D.S. R.C.S.
Professor of dental medicine in the University of London at Guy's Hospital.

M.V.O. (Fourth Class)

Wing-Commander HERBERT BRIAN KELLY, M.D. Lond., R.A.F.

O.B.E. (Military)

Surgeon Commander CLIFFORD VIVIAN HARRIES, M.R.C.S., R.N.

Surgeon Commander ROBERT ADAMS MCKEOWN, M.B. Belf., R.N.R.

Wing-Commander JOHN ERSKINE MALCOLM, M.B. St. And., R.A.F.

O.B.E. (Civil)

JOHN ADAM, M.B. Glasg.
Regional medical officer, Ministry of Health.

WLADYSLAW DERING,
Senior medical officer (surgical), Somaliland Protectorate.

JOHN DIXON, L.R.C.P.E.
Chairman, St. Albans medical board.

HUGH RICHARD JARVIS DONALD, B.M. Oxon.
Physician, public hospital, Christchurch, New Zealand.

CYRIL FORTUNE, M.D. Melb., F.R.A.C.P.
For services to the blood-transfusion service, Western Australia.

GEOFFREY DESMOND GORDON, M.R.C.S.
Senior medical officer, Ministry of Pensions and National Insurance.

ROBERT FRITZ HERRIES HINRICHSEN, M.D. Brazil, F.R.C.S.
Medical director, Strangers' Hospital, Rio de Janeiro.

LEONARD CATESBY HUGGINS, M.B. Edin.
Medical officer and bacteriologist (senior surgeon), Bahamas.

TREVOR CLAUDE JAMES, M.B. Melb.
Commissioner, St. John Ambulance Brigade, Tasmania.

WINIFRED BARBARA MEREDITH, M.B. Melb.
Director, maternal, infant, and preschool welfare, Department of Health, Victoria.

THOMAS MCCOWAT MONTFORD, M.B. Glasg.
Chairman, Leicestershire and Rutland executive council.

MILES PARKES, M.B. Manc.
Vice-chairman, Cheshire executive council.

CHARLES EMANUEL WILLIAMS, M.D. Melb., F.R.A.C.S.
Medical practitioner, Mackay, Queensland.

M.B.E. (Military)

Surgeon Lieut.-Commander DONALD CAMPBELL MCNUTT, M.B. Edin., R.N.

M.B.E. (Civil)

LEONARD EDWARD ARNOLD.
Pathologist, police department, Jamaica.

HECTOR MACKAY CALDER, D.S.O., M.C., M.D. Glasg.
Lately member, Glasgow National Service board.

WALTER WATSON FEATHER, M.B. Sydney.
Medical superintendent, Roma hospitals board, Queensland.

THOMAS DUNCAN GOULD, L.R.C.P.E., L.D.S.
British subject resident in Brussels.

MARY RAE KEYMER, M.B. Glasg.
Honorary physician, C.M.S. Hospital, Omdurman, Sudan.

MURIEL MILLICENT MANLEY, M.B. Lond.
Medical Officer of health, Kingston, Jamaica.

EDWARD HAMMOND WILLIAMS, M.B. Lond.
Medical superintendent, Kuluva Leper and General Hospital Arua, Uganda.

THE SOVIET MEDICAL SERVICES

THE purpose of the World Health Organisation's "public health paper" on Soviet Russia,[1] as of others in this new series, is to stimulate international thinking, discussion, and planning. It was prepared by medical and public-health representatives of 21 different countries (not including Western Europe or the United States) who, in October, 1958, made a five-week tour in the U.S.S.R., organised by W.H.O.

Clearly written with well-arranged headings, it is based on an official publication of the U.S.S.R. Ministry of Health, and it describes the structure of the Russian health services after 40 years of development, experience, and research. The object of the complex but unified organisation is to provide comprehensive medical care for the whole population, with central supervision but peripheral operational freedom, and integration of prevention and treatment. The three main sites of medical care are (1) central highly specialised institutes; (2) city hospitals, with policlinics and district units attached; and (3) rural hospitals, connected with district hospitals and policlinics. Diagrams at the end of the report illustrate clearly the structure of the medical services as a whole and also of a rural medical district, of a city hospital, and of a factory medical and sanitation department.

The separation of adult from child medicine (and of hygiene from both) is described, together with other striking characteristics of Soviet medicine such as the large amount of time and money spent on "prophylaxis" and on physical methods of treatment, in rest homes and health resorts. The hours worked by doctors and nurses, the number of hospital beds for different specialties, the importance attached to maternal and child health, occupational health, and sanitation, and the special provision made for infectious and chronic illness are also mentioned.

Six pages are allotted to medical education (undergraduate and postgraduate); two to the training of nurses, midwives, feldshers (assistant doctors), and technicians; three to health education of patients; two to research; and one each to mental health and vital statistics. A doctor now visiting Russia tells us that he found the booklet very useful as an introduction to what he was to see.

1. Health Services in the U.S.S.R. World Health Organisation public health paper no. 3. 1960. Pp. 58. Obtainable from H.M. Stationery Office, at 3s. 6d. Also published in French.

Occasional Survey

"FAULTS", "HITS", AND AGEING

THE PROCESS by which we—and other animals—lose vigour with age has an attractive mathematical regularity. This may be advantageous for life assurance, but it is also responsible for a vast number of attempts to settle mathematically a problem which, in the long run, can be settled experimentally and in no other way, most of them made by *savants calculs* of a metaphysical cast of mind, or by mathematicians without biological experience. This historical background accounts for the exasperation with which experimental gerontologists are apt to regard speculative papers explaining ageing in terms of the shape of the survival curve; and the apprehension with which many view the latest irruption of physicists into the subject, following the discovery that low doses of radiation appear to accelerate ageing.

The most recent of these mathematical attempts, by Szilard,[1] evokes some of these reflex responses; but it differs radically from the *savant calcul* tradition in identifying mathematical properties with tangible and measurable biological facts, and in suggesting experiments to verify the speculation. In the face of the evidence from radiation experiments[2] some such theoretical attempt had to be made, and gerontologists conducting survival studies have been looking at their results to see how far Szilard's theory fits them.

Szilard starts by assuming that the elementary step in the process of ageing is a "hit" (not necessarily by a radiant particle) which renders all the genes on one chromosome of a somatic cell inactive. "Hits" are random events, the probability throughout life of any one chromosome being "hit" is constant, but the rate of occurrence of "hits" is characteristic of the species. As a result of these "hits" the proportion f of somatic cells which are still functioning properly declines with age, until it reaches a value f^*, at which point the probability of dying within the next year approaches unity.

At the same time, every individual is assumed to carry a load of genetic "faults". A "fault" is a mutation in one of the genes essential to the proper working of a somatic cell. (In man, Szilard assumes that 3000 out of a probable 15,000 genes are essential in this way.) A cell ceases to be able to function when both members of the gene-pair for any one of these "vegetative" genes are out of action. Accordingly, when a chromosome suffers a "hit", the cell will cease to function (a) if the homologous chromosome has already suffered a "hit", or (b) if it carries the corresponding "fault" at a vital point.

This, then, is the model: by assuming probable values for quantities which nobody knows, Szilard proceeds to derive plausible approximations to the observed values of quantities which we do know, such as the concordance between twin ages of death. He also proposes, not an experimental proof, but a critical experiment—the reduction of life-span in the F_1 born to irradiated male mice, which was observed after some of the American bomb experiments,[3] could support or negative the mathematical model.

1. Szilard, L. *Proc. nat. Acad. Sci.* 1959, **45**, 30.
2. Comfort, A. *Radiation Res.* (Suppl.), 1959, **1**, 216.
3. Russell, W. L., Russell, L. B. *ibid* p. 296.

The model itself has a number of other important implications. One is that if m, the number of chromosome pairs, is different for two different species, the specific life-shortening due to a dose of radiation will be greater for that in which m is the smaller, and will vary inversely as $\sqrt{m}$. Szilard also works out, on the assumption of an average in human females of $n = 2{\cdot}5$ inherited "faults" per head, the modal longevity of a genetically perfect female with no such "faults": it comes to 92 as against the present 80 years. If n were greater it would be more. He also concludes that at the gloomiest estimate the load of "faults" cannot double in less than 25 generations from any cause; for $n = 2{\cdot}5$ this doubling would represent a loss of longevity of 15 years.

As Ernie Pyle would say, "the first word which comes to mind is But"—particularly to biologists working on age processes and aware of their probable complexity. At the same time, this kind of mathematical simplification cannot be rejected out of hand, because it has often worked surprisingly well—Morgan's assumption that the genes on a chromosome are arranged in a straight line and behave accordingly is a case in point. Such models can cut the Gordian knot or merely tangle the subject further. The essential for Szilard's model to be relevant seems to be that ageing should be timed by a fault in replication following the loss of an allele which is essential to a single cell. If his model fits universally, or at least well, and goes on doing so when "probable" are replaced by observed quantities, it would support this idea. The two most immediate criticisms were made almost as soon as the theory appeared,[4] and answered, or accommodated, by its author. The first is that if the theory of "faults" is correct one might expect the vigour of inbred and homozygous animals to be greater than that of hybrid or heterozygous animals, whereas the reverse is almost universal. The second concerns his "probable" values. The only reason for Szilard's assumption that a "hit" inactivates one whole chromosome seems to be the need to find a quantity of the right order of magnitude to account for the difference observed, for example, between male and female longevity, there being too many genes and too few cells to yield sensible results, while the human chromosome number is conveniently situated between the two.

It is also difficult to relate Szilard's theory as it stands to the dynamics of cell-division, for it makes no distinction between the effect of chromosomal "hits" developing in cells of which the population is fixed from birth, in high-turnover cells, and in stem cells where "faults" acquired by point mutation and "hits" will both affect cellular progeny. Vertebrates are a mosaic of all three types of cell. If Szilard's critical proportion f^* represents a fraction, not of the cell numbers but of an unspecified stuff "vitality", his further equations only restate the accepted actuarial pattern in different terms: to make them experimentally useful, ageing must be timed predominantly by loss of irreplaceable postmitotics—neurones, perhaps, or endocrine cells unspecified; or by a process with the same mathematical properties. The idea of ageing by essential cell loss is an old one: it can by no means be excluded as a cause of mammalian ageing, while for the ageing of forms such as insects, which have a low cell turnover, or rotifers, which have none, it seems very probable. It might also apply to special organs or contexts (Szilard's "special vegetative" processes) which contribute to ageing by their failure: it already looks, for example, as if the senescence of the human ovary may be due to running out of oocytes.

If human ageing were indeed timed by the loss of key postmitotics, the Szilard theory would become at least plausible. The effects of radiation which are said to accelerate ageing must then presumably be on postmitotic chromosomes or their products—a subject on which nobody seems to have much information. But as a rule non-dividing cells, and animals composed of them, are notoriously insensitive to radiation damage. In this respect the word "hit" is misleading, however, because of its radioactive implications. *Loss*, or rather constitutional absence, of a chromosome has become a more familiar concept in the last few months than ever before, with the discovery of human aneuploids suffering varying degrees of disability. If, as the equations seem to require, the unit of a "hit" is a whole chromosome, loss, or some other non-radiological disaster which might not be visible, is a more likely expectation. If neurones or the like are involved, there are in any case no outward and visible chromosomes in the mitotic sense to be hit, and the process envisaged must be analogous to the decay of teeth in the Cheshire Cat's grin.

There is another and far more interesting possibility, however, involving mutation in its more usual sense and confined to a single cell system, to which Szilard's mathematical intuitions might possibly be found to apply. Immunologists now seem to accept that the power to produce each individual antibody is acquired initially by an individual lymphocyte and transmitted to its progeny. A mechanism, not fully understood, determines that lymphocytes shall not normally respond to their proprietor's body-constituents by forming antibodies against them. Burnet has recently suggested[5] that if mutation in lymphocytes is capable of affecting this negative specificity, the organism must face a steady increase in autoimmune reactions with the passage of time—reactions which are likely to be of precisely the variable, diffuse, and polymorphic type which might explain the natural history of ageing as seen in man, while the statistical constancy of the mutation-rate and/or the rate of occurrence of Szilardian "hits" remains to provide the basis of life assurance.

This idea, that the organism comes with time to have more and more cells producing substances inimical to its own tissues, is an unexpected revival of Metchnikov, who always predicted that the same cellular mechanisms would turn out to be morphogenetic in the embryo, immunoprotective in the adult, and actively destructive in the end. The application of Szilard's scheme to such a system calls for some thought, but it appears at first sight to fit rather well, or at least better than most. The effect of a "hit" is in this case not that it removes a cell from useful activity, but that it puts one, and probably also its progeny, into destructive activity; and f^* is no longer a proportion of an original cell capital below which we are bankrupt, but something more like a median lethal dose. Meanwhile, Burnet's theoretical argument demonstrates quite plausibly that something of the kind ought to take place. What is still lacking, however, is experimental evidence that it really does so.

ALEX COMFORT.

4. Maynard Smith, J. *Nature, Lond.* 1959, **184**, 956; Szilard, L. *ibid.* p. 958.

5. Burnet, F. M. Croonian lectures to the Royal College of Physicians, 1959.

In England Now

A Running Commentary by Peripatetic Correspondents

THE retired G.P. will find numberless uses in the garden and the house for the tools of his trade. Forceps of various types for pricking out seedlings or retrieving dentures, rings, and other precious objects from "down the plug-hole"; "cut-throat" razors for layering or grafting; tourniquets for fractured boughs, and so on. Some weeks ago a blue tit began to build in the wooden letter-box of our weekend cottage, as it had done in two previous springs, in spite of a perfectly good nesting-box alongside and arrowed notices "Tits here", and "Letters here"—one would almost think they could not read. Two weeks later there were eggs, but a letter had meanwhile been delivered and incorporated in the nest. I was concerned about the letter and my wife about the disturbance to the nest which its extraction would inevitably cause. The problem was solved by examination with a laryngeal mirror which revealed a brown twopenny stamp. Clearly we need lose no sleep over a receipt or a demand for the rates. The Uckfield R.D.C. or the P.M.G. could surely wait, and meanwhile the postman obligingly put other communications under the door. Alas for human ingenuity and cooperation! Last weekend the door of the box stood open, the nest was scattered over the lawn—the letter proved to be an advertisement for Shetland wool with samples—and two moribund young tits were all that remained of the family. It was late evening and the remnants outside were cleared up and the door of the letter-box shut on what was left and on the young tits, now dead. Next morning the door was open, the bodies had vanished and the remaining nesting materials scattered around. Was it some Ruthless Rat, some Faceless Chinese Badger, or (my own theory) a Pockmarked Mexican Grey Squirrel?

* * *

"You told me there would be nothing to it, doctor, just a small operation, you said. You didn't tell me about the night before, with me lying there and my heart thumping, listening to the coughing and the snoring, and watching the nurses at the end of the ward. It was just light when they came and took my teeth out, and took my rings off and me worn them night and day for these last thirty years. Then they put me on a cold, stiff nightdress. 'No breakfast for you this morning, dear,' they said. The other patients drank their tea and smiled. 'You'll be all right. There's nothing whatever to worry about. Well good luck anyway,' they said. 'Come along there, Nurse Binks,' said the sister, 'you should have had her away half an hour ago.'"

* * *

When I admit a woman from outpatients I have often had to ask the Almoner to find somebody to look after half a dozen small children; but last week's patient said "I run a riding-school single-handed. Who will look after my twenty horses, three cows, and a dog?" The Almoner had no idea which end of a horse was which, and she could think only in terms of children's homes. So I had a rapid course on breast-pumps from the Obstetrician, and the problem of the milking of the cows seemed to be settled. My small daughters have a pony and it was, therefore, decided that, as an expert on the feeding and mucking-out of one small riding pony, I could easily look after twenty horses.

Fortunately, the patient was able to go out in a couple of days, and I can now appear in the hospital without straw in my hair and no longer smelling too strongly of the gardener's friend!

* * *

Today I saw a lorry that came from Denton. It took my mind back to the days when I worked in Manchester and had my car serviced in Denton at a remarkable garage which had evolved from the local smithy. It was full of anvils and old cartwheels, and there was an open fire in the middle of the floor. The owner was unsuitably named Clarence: he was a tough, stocky, curiously old-fashioned fellow who had a fund of wise saws. If I complained of a noise in the engine, he would say: "Ah well, where there's noise there's power."

Once, when a three-day job was needed on my car, I asked Clarence if he would lend me one in the meantime. Those three days must have narrowed my coronaries considerably. The ancient car had no brakes at all, only two gears (first and fourth), and no lights to speak of: but there was a system for "audible warning of approach". To sound the horn, you picked up a piece of wire that hung loose from the dashboard and applied the end of it to any convenient piece of metal. I was scared stiff of electrocuting myself.

When I turned up at the end of the third day, Clarence showed signs of relief. I imagined he had feared for my safety, but I was wrong. "Y'know," he said, "I'm right glad to see you: I was beginning to feel ashamed to think of a doctor riding about in yon. It oughtn't by rights to be on the road at all." The respect that he put into the word "doctor" came straight out of the 19th century. It made me think I should be inquiring whether he'd finished the work on my buggy.

* * *

Looking through my small daughter's exam-papers I came on a thing called a gerund. It seems to have something to do with parts of speech, and I can swear it was no part of anything in my day: I had never heard of it before. Fishing for information I remarked that "you don't see many gerunds around nowadays", and when this produced no reply I tried "I think they've given up gerunds on the telly". Retiring baffled I tried my wife with "They do teach gerunds very early nowadays", and only got a cold look for my pains. Deciding to play this game more dodgy-like, I tried the public library with "a book on parts of speech please", to be met with "which part would you like?" This was a teaser as I always thought there was only one part. However, as a final gambit I managed a "which part do you usually have?" This was stalemate with honours even. Next time I'll go it alone. If I start with autobiographies and work my way through hobbies to geography, by this time next year I should have struck oil and gerunds.

* * *

It isn't always an advantage to have a brother ahead of you in medicine. Brother George, two years my senior, once said to me, "Now, Bill, some time in the biology class the lecturer will announce, 'Today, we are going to study the botany of the apple, the berry, the rowan, and the haw'. You be ready for him and shout out, 'Haw Haw'." I thought that would be great fun and eagerly awaited the day. At last it came, and as George had predicted the lecturer, with seeming deliberation, said, "Today we are going to study the botany of the apple, the berry, the rowan, and the haw." He seemed to pause, so that I had plenty of time to shout out "Haw, Haw." After the laugh had died down he said, "Ah, yes, the annual donkey."

However, I got my own back on brother George. I followed him into a house job and also into his place in the pack of the local rugby team. I played well in my first games and the local newspaper published a note about my play in the sports column. I sent it, with love, to brother George. It ran, "Dr. P . . . is having his second season with the town team, and is a greatly improved player from the form he showed last year."

* * *

A MATTER OF TIME

So, here you see me: Cast away
My brief Combustion ended, all my Fire
In one last plume of Smoke must now expire.
Others have been before me, said their say,
Have kissed those self-same Lips this very day
And gone; his Breath will yet inspire
A Dozen others like me. Not Desire
But mutual Death is in our fleeting Play!

What though he is the Master and 'twas Men
Created us, the lesser partners in the Game?
It is too early yet for him, poor Fool, to boast;
A Hundred Thousand of us may be Ash by then
But Twenty years from hence it will be all the same—
And who, I wonder, will have lived to suffer most?

Letters to the Editor

"METABOLIC INSUFFICIENCY"

SIR,—Your editorial,[1] Goodbye to "Metabolic Insufficiency" made the strong inference that the last word had been written concerning this controversial syndrome, and further investigation had better be abandoned lest euthyroid hypometabolism (a preferable title) be denied its "quiet disappearance from the medical literature". Unfortunately the argument cited, the report by M. E. Levin—based on a "double-blind" study conducted on only 6 patients—hardly supports such a decisive stand.

One might gather from the editorial comments of several of the medical journals that the "double-blind" study has become a modern-day Holy Grail, relegating less ambitious researchers to ignoble ends. Be this as it may, one all-important factor which must be firmly established—particularly when a hormone is used in a "double-blind" study—is proper and adequate dosage. One can easily imagine the opportunity which might have been missed had Best and Banting decided to put 5 units of insulin to the "double-blind" test in the treatment of diabetes. One might also recall the erroneous conclusions reached in the British study comparing salicylates and cortisone (100 mg.) in the treatment of acute rheumatic fever. The experience of Kurland, Hamolsky, and Freedberg, as well as my own in 32 cases, has clearly shown that the majority of "hypometabolic" cases require a minimum daily dosage of 100 μg. triiodothyronine, and even then there is usually a time lag of two or three weeks before subjective or objective improvement is observed. Thus, considering that a final dosage of 75 μg. was given by Levin, and this for only two weeks in one-third of patients and four weeks in two-thirds, it is hardly surprising that his results were equivocal. The time-lag in the euthyroid hypometabolic patient before triiodothyronine affects the basal metabolism is in striking contrast to the prompt metabolic response to triiodothyronine in three to five days in cases of true hypothyroidism.

During the past three years, approximately 500 patients have been screened in our endocrine clinic for euthyroid hypometabolism; the majority of them were suspected of being psychoneurotic or hypothyroid. Among this group, 32 patients (6·4%) were believed to have euthyroid hypometabolism as judged by the following diagnostic criteria:

(1) A symptom-complex resembling hypothyroidism in certain respects and psychoneurosis in others.

(2) Presumably normal thyroid (thyroxine) function as shown by a normal protein-bound iodine value (P.B.I.) and a normal rise in P.B.I. following the administration of thyrotrophic hormone.

(3) Objectively, a B.M.R. below minus 10% and a prolonged electrometric recording of the free Achilles reflex. [2]

(4) No response to placebo or desiccated thyroid, the latter given in daily dosages up to gr. 5 or intolerance.

(5) A favourable response, both objectively (B.M.R. and reflex recording) and subjectively, to proper amounts of triiodothyronine—on the average of 100–125 μg. daily—and maintenance of such improvement over a minimum follow-up period of six months.

Previously a major drawback to screening patients for hypometabolism has been the absence of an objective parameter of end organ metabolism, which is consistently abnormal in such cases, and of a higher degree of accuracy, reliability, and reproducibility than the conventional B.M.R. procedure. (Only 50% of B.M.R.s were abnormally low in these 32 cases when done for the first time. The majority of patients had B.M.R.s recorded on three consecutive days.) This situation has been remedied by the finding that the contraction phase of the Achilles reflex (as measured electrometrically by the Lawson apparatus) is significantly prolonged in both hypothyroidism and euthyroid hypometabolism in over 90% of cases, and that such an abnormality is only rarely encountered in other diseases affecting metabolic or neuromuscular function. Furthermore, neither the B.M.R. nor reflex recording shows improvement in truly euthyroid hypometabolic patients given desiccated thyroid or placebos or positive suggestion, but returns to normal levels when triiodothyronine in adequate doses is given. Since the "hypometabolic" patient often masquerades clinically as a psychoneurotic and is usually misdiagnosed as such, and since triiodothyronine is completely effective in relieving the so-called "psychoneurotic" complaints in the vast majority of "hypometabolic" patients, it seems well worth screening such patients for hypothyroidism or euthyroid hypometabolism and thus spare them the fate of the true neurotic—dependence on tranquillisers or prolonged expensive psychotherapy.

The relationship between euthyroid hypometabolism and "neurotic" behaviour is probably more than a casual one, although a precise cause-and-effect mechanism remains unknown. In fact, considering that all the tests of the functional capacity of the thyroid gland itself (in contrast to end organ metabolism) have been found to be within normal limits in the euthyroid hypometabolic patient, the possibility remains that this syndrome is not a thyroid disease at all, but results from some cortico-hypothalamic factor or bodily dysfunction which affects the thyroid gland—particularly the formation and release of triiodothyronine—only secondarily, as happens, for example, in hypopituitary myxœdema. In summary, it is my present belief and experience that a syndrome of euthyroid hypometabolism does, in all likelihood, exist and is worthy of further consideration and study—particularly, as to its pathophysiology and incidence among patients with psychodynamic complaints. The study conducted by Levin should be regarded as a praiseworthy and important contribution to this enigma, but hardly the last word. The scepticism professed by *The Lancet* concerning the unsettled existence of euthyroid hypometabolism is looked upon as healthy and challenging, but an obituary is decidedly premature.

Worcester, Mass. MARSHALL GOLDBERG.

*** Our annotation was intended as a challenge to those who believe in the existence of this syndrome, and we are delighted that Dr. Goldberg has responded. He rightly points out that a "double-blind" trial is not ipso facto sacrosanct and is often open to criticism on other grounds. Nevertheless, it seems to us that no firm conclusions can be drawn about the effects of therapy in a condition which "often masquerades as a psychoneurosis" (Dr. Goldberg's words), unless a double-blind procedure is employed. The obvious answer to our criticism would be for Dr. Goldberg to repeat Levin's observations, using the dosage and duration of therapy which he considers adequate. Until he has done so (and there is no indication in his letter that he has), we feel justified in reserving judgment on his claim that "triiodothyronine is completedly effective in relieving the so-called 'psychoneurotic' complaints in the vast majority of 'hypometabolic' patients".—ED. L.

CAUSE OF ŒDEMA IN "COR PULMONALE"

SIR,—In their article of May 28, Dr. Campbell and Dr. Short state that œdema in chronic lung disease is not closely correlated with a raised venous pressure. An absence of the urinary abnormalities of heart-failure (high specific gravity, proteinuria, cells, and casts) [1] is further evidence against attributing the œdema in these cases to myocardial failure. Similarly, abdominal palpation may fail to show the signs of passive venous

1. *Lancet*, Feb. 27, 1960, p. 480.
2. Lawson, J. D. *New Engl. J. Med.* 1958, **259**, 761.

1. Segall, J. J. *Lancet*, 1953, i, 524.

Case no.	Sex	Age	Ætiology	Increased jugular venous pressure	Palpable liver	Hepatic tenderness	Ascites	Proteinuria	Œdema
23	F	76	Presumed ischæmic heart-disease: auricular fibrillation, left ventricular enlargment, B.P. 120/70	+	+	0	0	0	+++
25	M	65	Presumed ischæmic heart-disease: auricular fibrillation, B.P. 130/70	+	+	0	0	0	+++
28	F	81	Presumed ischæmic heart-disease: sinus rhythm, B.P. 190/90	+	0	0	0	0	+++
29	M	63	Pulmonary heart-disease due to chronic bronchitis and emphysema: sinus rhythm, B.P. 160/80	+	+	0	0	0	+++
49	F	50	Pulmonary heart-disease: right ventricular enlargement, auricular flutter, B.P. 140/100	++	+	Not recorded	0	0	+++

0=absent +=slight ++=considerable +++=massive

congestion of the liver—namely, tender hepatic enlargement and ascites.

The occurrence of preponderant œdema with minimal venous congestion is not entirely limited, however, to cases of anoxic pulmonary heart-disease. In an unpublished series of 52 cases of heart-failure, such disproportionate œdema was present in 5 instances, of which 3 could not be regarded as cases of chronic cor pulmonale. The salient features of these 5 cases are shown in the accompanying table; recovery from the attacks occurred with conventional treatments.

The suggestion of Campbell and Short that hypoventilation and increased work of breathing may be factors in the production of œdema in cor pulmonale could apply also to other dyspnœic patients who develop preponderant œdema; in elderly patients, for example, atrophic emphysema could play a similar role in the genesis of the œdema. The importance of increased work of breathing in the production of cardiac œdema has received a therapeutic confirmation in a recent report that tank-respirator treatment alone may cause elimination of œdema in decompensated cor pulmonale.[2]

London, N.W.2. J. J. SEGALL.

FLUORIDATION

SIR,—Lord Douglas of Barloch (June 4) draws attention to the finding, by the Councils on Drugs and on Foods and Nutrition of the American Medical Association, that there was a statistical difference in the deaths at Bartlett and at Cameron and suggests that it may be that the Ministry of Health "does not consider death to be an important effect".

The original report on Bartlett and Cameron came from the National Institute of Dental Research in 1954 and 1955 and stated that there were no significant differences between the age-adjusted death-rates in the two towns, and the Ministry of Health paper was dated 1955. Using a different, more exact, method of statistical analysis, the Councils quoted above later found that "the odds are approximately 1 in 21 that mere chance determined the difference ($p=0{\cdot}048$)."

This point is only made here to answer Lord Douglas' insinuation that the Ministry may view death callously. The real question is whether the difference was in fact due to the fluoride in the Bartlett water, or to some other difference between the two towns; in other words, whether it was an important effect in the context of the Ministry of Health's reference note which deals with fluoridation. Here, Lord Douglas omitted the ensuing sentences from the Councils' report: "This one comparison, however, must not be given undue weight. Roholm's view on general toxicity has just been quoted; his cryolite workers probably had more than twice the fluoride exposure of the Bartlett residents". Roholm states (and here we pass to the preceding page of the Councils' report): "There is nothing to show that working with cryolite reduces the period of life or that cryolite workers acquire macroscopically recognisable organic lesions apart from the bone changes". The Councils' view on Roholm's work, which was published in 1937, was that it "is still the most detailed and reliable on chronic fluoride poisoning".

I could advance further evidence to support the view that the higher death-rate at Bartlett was not due to fluoride, but I am very conscious of the space which has already been occupied by this correspondence. Suffice it to say that the board of trustees of the American Medical Association House of Delegates, after study of the Councils' report, reached the opinion that "fluoridation of public water supplies is a safe and practical method of reducing the incidence of dental caries during childhood".

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SEX CHROMATIN IN SOMATIC NUCLEI

SIR,—Reconstructions of Feulgen-stained serially cut human and rodent somatic cell nuclei have made it likely that all the chromatin masses which are seen in nuclei as seemingly free and discrete features are in fact nucleolar associated chromatin.[1] In fixed preparations the chromatin covers the nucleoli as one or more caps which when sectioned may appear as unattached chromatin masses. As the nuclei are randomly orientated with respect to the direction of the cutting the chromatin masses may seem to be randomly distributed, and the frequency with which a given chromatin mass is observed in a given position is therefore determined by the ratio between the dimensions of the feature and the nucleus.

It is stated [2 3] that the female sex chromatin is approximately 1μ "in diameter", located on the inside of the nuclear membrane, and found with a frequency of 60–80% in 5μ-thick sections of female somatic tissue and with a frequency of 5–10% in male nuclei. If the sex chromatin is synonymous with the XX-chromosome there can only be one such feature per somatic female cell nucleus. If this were so the frequency with which it would be observed in its characteristic locations in sections would be about 40% if the nuclear diameter was as small as 7μ, and the frequency would be even lower if the nucleus were bigger. The observed frequency of 60–80% suggests that more than one "sex chromatin" body exists in the female nucleus. If this is so, the morphologically recognisable "sex chromatin" might be interpreted as evidence that the nucleus is female and therefore possesses the XX-chromosome, but that this is not synonymous with the "sex chromatin". The findings are, however, fully explicable if we assume a difference on a molecular level in the template-replica system between male and female nuclei. And the observed differences

2. Effersöe, P., Kristensen, H. S., Lassen, H. C. A. *Brit. med. J.* May 14, 1960, p. 1469.

1. Iversen, S. *Acta anat.* (in the press).
2. Barr, L. M. *Science*, 1959, **130**, 679.
3. Lennox, B. *Scot. med. J.* 1956, **1**, 97.

in morphology between male and female nuclei of some species may thus indicate secondary sexual characteristics at the level of the nucleus.

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Glasgow. SIMON IVERSEN.

FLACCID QUADRIPLEGIA FOLLOWING URETERIC TRANSPLANT

SIR,—I was interested to see Dr. Angeloni and Dr. Scott's article of May 7 on hypokalæmia in a patient with ureteric transplant, in addition to the more commonly recognised hyperchloræmic acidosis. We have found this to be a relatively frequent occurrence; in a series of 93 patients over half had hypokalæmia at some time, and in a few cases where full balances were done as much as 600 mEq. K was retained before the plasma levels returned to normal. These results are to be published later. In some cases the K deficiency was not obvious from the plasma figures until the acidosis was corrected, so it may be even more common than is generally realised.

Incidentally, this article contained an excellent example of the confusion and inconvenience arising from the use of several systems of weights and measures. The patient received 3 litres 0·1% KCl and "mist. pot. cit. *B.P.C.* 1/2 oz. four-hourly", while his plasma-K was 1·5 mEq. per litre. It requires considerable manipulation with a slide-rule to discover that he had received over 170 mEq. K per day, which after all is the essential information required for treatment, or should be.

Biochemistry Department,
Glasgow Royal Infirmary. ALISON J. DINWOODIE.

NAMES OF DRUGS

SIR,—I agree with Colonel Walton (June 4) that the nomenclature of drugs would benefit by simplification. Practising doctors and their patients must indeed be grateful to the research chemists and the pharmaceutical firms who are providing such a wealth of potent remedies in so many fields, but the names do get baffling. May I offer a few suggestions?

1. An effort should be made to find official names which are shorter and less cumbersome. Three or four syllables should be the aim, and five should be the maximum. Phthalylsulphathiazole, cyanocobalamin, and hydroflumethiazide each have seven.

2. There should be less reluctance to adopt a new shorter name for a drug which is proving really useful. Why should not phenobarb be the official name instead of the abbreviation for 5-ethyl-5-phenylbarbituric acid? At least it would get rid of the confusion of the synonymous usage of the names phenobarbitone and phenobarbital. There can be few other amine derivatives containing cobalt of therapeutic importance, and to rename cyanocobalamin simply as cobalamin could hardly lead to difficulty.

3. An agreed series of monosyllabic euphonious prefixes could be established to indicate the various operations performed by chemists on molecules, such as removing or adding methyl, hydroxyl, or amine radicles, much as noradrenaline signifies adrenaline from which a methyl radicle has been removed. One or two syllables could then be saved on the "hydroxy", "dehydro", and "demethyl" derivatives of standard preparations.

4. Every manufacturer should be required, on all labels, pamphlets, and advertisements, to print the official name of a preparation in letters at least as large and as prominent as those in which the proprietary name is displayed.

5. A standard code of pronunciation would be helpful.

It is, of course, axiomatic that, before suggestions such as these could be adopted usefully, they would have to be agreed internationally.

Bedford General Hospital. R. G. MILLER.

CÆSAREAN SECTION AND HYALINE MEMBRANE

SIR,—According to Snyder [1], whose work is referred to in your leader of March 26, the high incidence of hyaline-membrane disease observed in full-term infants delivered by cæsarean section is related to aspiration of maternal blood. This implies that there is an increased danger of "contamination of the lungs by blood-laden amniotic fluid" in deliveries by cæsarean section. An attempt was made to test this suggestion.

In a series of 1020 consecutive deliveries, adequate smears of the stomach content [2] were obtained at birth in 960 newborn infants including 65 infants delivered by cæsarean section. The smears were examined microscopically for the presence of red blood-cells and classified in three groups according to the number of erythrocytes encountered. Since fœtal and immediately postnatal gastric juice is said to show a relative lack of acidity [3], the results are unlikely to be altered by hæmolysis of the swallowed erythrocytes. The control group consisted of the 130 normal spontaneous vertex deliveries immediately preceding and following the cæsarean sections. The smears were read blindly. A comparison of the two groups by the fourfold table

Amount of blood in gastric content	Cæsarean sections	Normal deliveries	χ^2	P
None or rare R.B.C. ..	50	90	0·003	>0·95
Moderate	9	23	0·79	0·5>P>0·3
Abundant	6	8	0·24	0·7>P>0·5
Total	65	130	..	..

method showed no significant difference in the incidence of blood contamination of the stomach content. 1 infant of the cæsarean-section group died at the age of nine hours. He was a 1500-g. premature and presented a moderate degree of hyaline-membrane disease. There were 4 stillbirths in the control group. All 5 dead infants had gastric aspirate rated "none or rare R.B.C.".

If one admits the reasonable assumption that the gastric content is fairly representative of the amniotic content, then "cæsarean-section babies" are not exposed more frequently than other babies to the aspiration of blood-laden amniotic fluid. Therefore, the increased incidence of hyaline-membrane disease after delivery by cæsarean section seems related to other, more complex events.

These results do not rule out the possible role of exogenous material as a subsidiary or contributing factor in the pathogenesis of the membranes. There is morphological evidence at hand supporting the exogenous pathogenetic theory, at least in some types of membranes. The "vernix" membrane [4], usually found in full-term infants, is made up of vernix caseosa containing squames and cellular debris and takes fat stains. The "fibrin" membrane is found within foci of hæmorrhage [5] or blood aspiration. It is limited to these areas and tends to be more refractile and eosinophilic than the typical "hyaline" membranes of premature infants. It takes ordinary fibrin stains, whereas special techniques are required to demonstrate fibrin in typical "hyaline" membranes [6]. The latter type is now considered a result of transudation [7–9] and merely the end stage of a complex process. The demonstration of aspirated material within the membrane [10–13] does not contradict the transudation theory. The "hyaline" membranes are distributed diffusely throughout all lobes, contain little or no fat, nuclear and cellular debris and show no consistent correlation with the presence of

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2. Blanc, W. A. *Clin. Obstet. Gynec.* 1959, **2**, 705.
3. Ebers, D. W., Smith, D. I., Gibbs, G. E. *Pediatrics*, 1956, **18**, 800.
4. Farber, S., Sweet, L. K. *Amer. J. Dis. Child.* 1931, **42**, 1372.
5. Landing, B. M. *Pediatrics*, 1957, **19**, 217.
6. Craig, J. M., Fenton, K., Gitlin, D. *ibid.* 1958, **22**, 847.
7. Tessereaux, H. *Frankfurt Z. Path.* 1949, **60**, 188.
8. Gruenwald, P. *J. Amer. med. Ass.* 1958, **166**, 621.
9. *Lancet*, 1958, ii, 945.
10. Ahvenainen, A. K. *Acta pædiat.* 1948, suppl. 35.
11. Blystad, W., Landing, B. H., Smith, C. A. *Pediatrics*, 1951, **8**, 5.
12. Blanc, W. A. *Arch. Sci.* 1951, **156**, 388.
13. Claireaux, A. E. *Lancet*, 1953, ii, 749.

aspirated material, inflammation, or hæmorrhage. They are rarely found in alveoli where "vernix" and "fibrin" membranes are less uncommon. In most cases, one sees also amorphous pale-staining albuminous material lying in alveolar ducts and atria. Although not found primarily in alveoli as in pulmonary œdema, stricto sensu, this material is similar to œdema fluid. Pulmonary lymphatic vessels are engorged and œdema is present in other tissues [14]. These generalised changes are associated with a definite clinical syndrome. It is not certain whether the membranes formed by air-bubbles in areas of œdema [5] should be distinguished from hyaline membranes since they may well represent an early stage of the latter.

At the present time the "fibrin" membrane is the only one definitely associated with the presence of blood in the bronchial and alveolar spaces. On the basis of the cytology of neonatal gastric content and of pulmonary morphology, it appears unlikely that intrapartum aspiration of blood is related to the formation of the typical hyaline membrane.

A variety of causes have been attributed to different conditions grouped under the all inclusive term of hyaline-membrane disease. If this term is to be retained at all, it seems that an agreement on a nomenclature of neonatal pulmonary membranes would eliminate some apparent divergences of opinion. This might, in turn, accelerate the shift of interest of morbid anatomists from the membranes, an end result, to the underlying causes of the "respiratory distress syndrome" and its humoral [15] and circulatory [16–18] aspects.

Department of Pathology, College of Physicians and Surgeons, Columbia University and Babies Hospital and Sloane Hospital, New York.

WILLIAM A. BLANC
PAUL P. GWYN, Jr.

SIR,—In your leading article one is impressed with the importance of blood constituents in the formation of hyaline membrane. It is a little surprising then that there is no reference whatever to the original work which showed that the membrane (both natural and experimental) contains hæmoglobin in abundance.[19 20] May I draw attention to the fact that our work was also the first to record the hyperkalæmia associated with the condition? [21]

Sudbury General Hospital, Sudbury, Ontario.

M. J. LYNCH.

CONFIRMATORY MEDICAL CERTIFICATE BEFORE CREMATION

SIR,—I should like to draw attention to question 3 of the confirmatory medical certificate required before a cremation. The question is "Have you made a post-mortem examination?" Now in this hospital (as in many others) necropsies on my patients are performed by the morbid anatomist, who is expert at the job, and not by myself; it follows I have to reply "No". But there is no other question on the certificate asking about post-mortems, so this negative answer might well be taken to mean that necropsy was not carried out at all. Surely it is more important for the medical referee, who checks the certificate, to know that a postmortem examination was in fact carried out, than to know who did it?

I understand these questions are statutory, so I put this difficulty to the Home Office, who replied "... there would appear to be advantage in providing this information in answer to Question 3 even if the information is additional to that required by the actual wording of the question". But would it not be better to alter the wording of the question, so as specifically to ask for this information?

Whipps Cross Hospital, London, E.11.

E. HINDEN.

AN UNUSUAL FORM OF OSTEODYSTROPHY

SIR,—An account of an unusual family with some form of osteodystrophy is given in your issue of June 4 by Dr. Stuart Barber; unfortunately his report is vitiated by the poor quality of the radiographic reproductions. As the classification of these cases depends to so great an extent on radiographic interpretation the value of such reports to students of rare dystrophies and dysplasias of bone is largely lost. Because they are such rarities, atypical cases such as Dr. Stuart Barber reports are of great interest, and their eventual recognition as clinical entities depends mainly on the correlation of isolated case-reports. Not every journal will extend the hospitality of its columns to such accounts which at present are of scientific rather than practical value; when they do so it is all the more important that radiographs are reproduced with the highest fidelity. Although they are admittedly more expensive, may I make a plea for the more generous use of special plates on future occasions?

Cambridge.

T. J. FAIRBANK.

MATERNAL INFLUENZA AND CONGENITAL DEFORMITIES

SIR,—Before I deal with the points raised by Dr. Trimble (May 28) I should like to make it clear that my part in the study on maternal influenza and congenital deformities was little more active or laudable than that played by a spectator on the 2*s*. (shortly to be 2*s*. 6*d*.) terraces in the victory of his favourite team on a Saturday afternoon. The credit for conception and execution of this interesting and important research lies with Dr. Coffey and Professor Jessop alone.

I am sure that the authors would be the first to agree that the Dublin study may have methodological faults, but I am not sure that selecting patients for inclusion in the case group on the basis of self-diagnosis is, as Dr. Trimble (Jan. 9) suggests, a fault of any moment.

Had it proved possible to establish the diagnosis serologically the distribution of patients between case and control groups might have been changed in one of two ways. First, it might have been found that some of the women replying in the affirmative to the question "Have you had influenza during this pregnancy?" had in fact suffered from something else, and if this something else was a teratogenic disease the validity of the results would certainly have been in doubt. The contemporary work of Meenan [1], however, suggests that influenza virus A was the only infective agent active to a significant degree at the time. Second, the control group might have been shown to contain women who had been infected with the virus, and on the evidence of Wilson [2] and Walker [3] and their collaborators it is highly likely that the latter would have proved to be the case. Yet despite this probable impurity, the mothers in the control group bore almost the same proportion of malformed children as those in an earlier Dublin survey [4] which had been conducted when there was no epidemic of influenza. Thus, the Dublin study showed that those mothers in the city who had influenza and remembered it (and were presumably therefore really incapacitated) bore a greater proportion of malformed babies than those who were well throughout their

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15. Usher, R. *Pediatrics*, 1959, **24**, 562.
16. Nodot, A. Thesis, Paris, 1958.
17. Shanklin, D. R. *A.M.A. Arch. Path.* 1959, **68**, 49.
18. James, L. S. *Pediatrics*, 1959, **24**, 1069.
19. Lynch, M. J. G. *J. Pediat.* 1955, **47**, 275.
20. Lynch, M. J. G. *ibid.* 1956, **48**, 165.
21. Lynch, M. J. G., Mellor, L. D., Badgery, A. *ibid.* p. 602.

1. Meenan, P. N. Personal communication to Coffey and Jessop (*Lancet*, 1959, ii, 935).
2. Wilson, M. G., Heins, H. L., Imagawar, D. T., Adams, J. M. *J. Amer. med. Ass.* 1959, **171**, 638.
3. Walker, W. M., McKee, A. P. *Obstet. Gynec.* 1959, **13**, 394.
4. Coffey, V. P., Jessop, W. J. E. *Irish J. med. Sci.* 1955, **6**, 30.

pregnancy, or those who were infected by the influenza virus and did not remember it (and presumably remained more or less symptom-free). When these facts are taken together, and it is borne in mind that the mothers made their "self-diagnosis" *before* they knew the outcome of their pregnancy, I do not see how Dr. Trimble can reasonably question the implications of the Dublin study (Jan. 9)—always provided that he does not extrapolate from women who felt ill from influenza in Ireland to women in more prosperous communities who had a subclinical infection.

Coffey and Jessop argue in their discussion that such teratogenic effect as may be associated with influenza is unlikely to be due to direct infection of the fœtus by the virus, and a comparison between their findings and those of Walker and Wilson lends support to this view. In my previous letter (April 30) I referred to some of the evidence which shows that the women attending the three Dublin maternity hospitals are an underprivileged group, and it may well be that in the case of influenza it is not the infecting agent itself, but the systemic disturbance of a severe infection in a woman who is already sorely taxed in supporting her pregnancy, which is the factor that damages the fœtus.

London School of Hygiene and Tropical Medicine, London, W.C.1. ROY M. ACHESON.

TREATMENT OF SALICYLATE POISONING

SIR,—I am grateful to Dr. Macdougall and Dr. Cameron (May 28) for their opinions concerning "the efficacy of curarisation in reducing hyperpyrexia caused by salicylate".

In my letter of May 14 I was not suggesting that curare itself lowers the pyrexia which frequently accompanies salicylate poisoning. However, when respiratory obstruction occurs, particularly when the patient is hyperventilating and in a state of tetany, the extra work invoked in breathing against resistance frequently aggravates the pyrexia. In the case recorded by Freier et al.[1] the secretions were removed and the relaxed tongue bypassed by means of curarisation, intubation, and controlled ventilation. This combination of factors, and not the curare alone, soon resulted in the temperature falling from 101° to 99·4°F.

I agree with their suggestions that the drugs used in the induction of hypothermia may have a place in reducing pyrexia. They would be most useful in those cases where the pyrexia is so pronounced as to endanger the life of the patient. I feel, however, that if the patient is curarised then this aim may be attempted by the application of ice bags. In this way the side-effects of other drugs would not complicate the picture.

Southmead General Hospital, Bristol. FRANK WILSON.

ANHIDROSIS AND HEATSTROKE

SIR,—In his letter last week Dr. Ladell discussed the sudden cessation of sweating during exposure to dry heat.

In my view this is due to fatigue or degeneration of the nervous supply of the sweat-glands. This is very common in the ageing and is found in all cases of disseminated sclerosis, nervous degenerations, and asthma, and in advanced liver and kidney diseases. Under wet heat with refrigerant fluids to maintain thermal balance in the cerebral circulation[2] the sweat-glands do not fatigue and can be kept continuously under secretion for as long as thirty days with skin temperatures at between 96°F and 100°F.

In my view the sweat-glands are activated by two mechanisms. By one, under dry heat evaporation acts as a refrigerator to maintain thermal balance. This is under nervous control as are also gustatory and cold sweats due to nervous tension. The other mechanism under wet heat at skin temperatures from 90°F to 115°F, acts directly on the sweat-glands and continues to act on the glands even if their nerve-supply is fatigued and unresponsive to nervous stimuli. This second method of activation of the sweat-glands is relevant to the treatment of heatstroke, where wet heat to reactivate the sweat-glands plus refrigeration of the cerebral blood-supply by cooling the head must give quick and direct relief.

Tunbridge Wells. E. F. ST. J. LYBURN.

IMMEDIATE TREATMENT OF CEREBRAL INFARCTION

SIR,—Following the paper by Dr. Barham Carter (Feb. 13) may I call attention to the treatment of the acute stage of cerebrovascular accident ("incipient apoplexy") by intravenous administration of aminophylline or of an analogous theophylline compound.

After twelve years of clinical trial I suggested[1,2] this treatment in 1948–49, and elaborated upon it in later publications.[3–10] In an important percentage of cases (35–80%) the slow intravenous administration of aminophylline abolishes within a few minutes the initial manifestations of cerebrovascular accident (hemiplegia and/or coma) *provided the injection is given in the first hour after onset of symptoms*. Soon after our first report confirmation came from several authors[11–18] and others.

Return of consciousness and/or disappearance of paralysis is sometimes so rapid that the experience has been described as "startling" or "dramatic". On the other hand, unlike similar attacks in hypertensive encephalopathy, general paralysis, or multiple sclerosis, the sudden restitution of cerebral function is uncommon in the natural history of cerebrovascular accident of arteriosclerotic origin.

Which conditions in the various forms of cerebrovascular accident are susceptible to be influenced by aminophylline? Vasomotor action and the relief of cerebrovascular spasm have been proposed as the mechanism involved. But it is now well established that, in contradistinction to the views prevailing two decades ago, aminophylline has in fact a vasoconstrictor action on the cerebral circulation; this, however, is true only for the *total* cerebral flow as estimated by the Kety procedure. Anyhow, for these reasons the clinical effect of aminophylline in cerebrovascular disease can hardly be related to vasomotor effects. The very fact, however, that this theoretical concept was initially linked with this treatment may have fostered in England and the U.S.A. a scepticism which prevented a clinical trial.

Another mechanism of action was first suggested by Jarisch.[19] Aminophylline increases the permeability of the blood-brain barrier and blood-eye barrier and greatly reduces intrathecal pressure. The increased permeability may enhance the reduction of œdema and the washing out of cytotoxic metabolites, both due to the existing ischæmia. The favourable effect of reduced intrathecal pressure under these conditions is obvious.

Reduction of cerebral metabolism[20] and the familiar stimulating and awakening action of aminophylline on central-nervous-system function have been proposed by others as the underlying mechanism of its effect in cerebrovascular accident.[21]

1. Freier, S., Neal, B. W., Nisbet, H. I. A., Rees, G. J., Wilson, F. *Brit. med. J.* 1957, i, 1333.
2. *J. Physiol.* 1956, **134**, 207.

1. Mainzer, F. *Therap. Umschau (Berne)*, 1948, **5**, no. 2.
2. Mainzer, F. *Schweiz. med. Wschr.* 1949, **79**, 108.
3. Mainzer, F. *Med.Klin.* 1951, **46**, 938.
4. Mainzer, F. *Münch. med. Wschr.* 1952, **94**, 1724.
5. Mainzer, F. *Sem. Hôp., Paris*, 1953, **29**, 163.
6. Mainzer, F. *Verhdlg. Dtsch. Ges.Kreislaufforschg.* 1953, **19**, 246.
7. Mainzer, F. *Nervenarzt*, 1953, **24**, 278.
8. Mainzer, F. *Acta med. scand.* 1953, **146**, 362.
9. Mainzer, F. *Dtsch. med. Wschr.* 1954, **79**, 37.
10. Mainzer, F. *Alexandr. med. J.* 1956, **2**, 13.
11. Schimert, G. *Med.Klin.* 1950, **45**, 1038.
12. Schimert, G. *Dtsch. med. Wschr.* 1951, **76**, 1176.
13. Schlegel, A. *Berl. Aerztebl.* 1951, **64**, 17.
14. Schlegel, A. *Therap. Gegenwart.* 1952, **91**, 212.
15. Schmidt-Voigt, H.-J. *Med. Welt.* 1952, **20**, 1090.
16. Dimitrijevic, D. T. Personal communication, 1952.
17. Stockert, v. F. G. *Nauheimer Fortbildungslehrg.* 1953, **14**, 44.
18. Novotny, K. *Wien. klin. Wschr.* 1953, **65**, 1017.
19. Jarisch, A. Personal communication, 1952.
20. Müller, R., Schild, W. *Münch. med. Wschr.* 1955, **97**, 1060.
21. Perlick, E. *ibid.* 1957, **99**, 877.

Whatever the mechanism, ten years' experience of many workers in Europe fully justifies a trial of intravenous aminophylline in incipient cerebrovascular accident.

Swiss Hospital,
Alexandria, Egypt,
United Arab Republic. Fr. MAINZER.

RENAL HYPERTENSION

SIR,—Your leader of May 7 has unique significance for the obstetrician interested in the ætiology of toxæmia. In the first instance it has shown that evidence derived from the experimental animal has an actual counterpart in human disease; and, secondly, that renal ischæmia can account for a reduced urinary volume and an abnormally low concentration of sodium in the urine from the experimental kidney.

The animal researches of Mueller et al.[1] had already demonstrated this, and Howard et al.[2] have used these urinary changes as a means of clinical identification of the ischæmic kidney involved in renal hypertension.

Mueller divided his experiment into certain stages. In the earlier, *light* constriction of one renal artery of a dog caused in that kidney a marked decrease of sodium and water excretion without detectable falls in glomerular filtration-rate or renal plasma-flow, while in the later, *heavy* constriction produced a further fall in sodium and water output *and* a decrease in glomerular filtration-rate and renal plasma-flow. Howard's clinical and biochemical findings have demonstrated a fall in sodium and water output, while Shackman and Graber,[3] in their studies on divided renal clearance studies in hypertension, confirmed the decrease in glomerular filtration-rate and plasma-flow. Unilateral renal ischæmia has been shown, therefore, both in animals and in man, to cause hypertension, to lower the glomerular filtration-rate and renal plasma-flow, and to diminish the excretion of salt and water, thereby providing a potential cause of œdema and hypertension.

Fajers,[4] by imposing short periods of unilateral renal ischæmia in animals, caused proteinuric substances to appear in Bowman's capsule, thus in turn supplying an explanation of albuminuria.

Byrom,[5] in his very important researches in rats, has further shown that unilateral renal ischæmia, effected by the Goldblatt clamp, produces both hypertension and hypertensive encephalopathy as a result of cerebral vascular spasm—conditions that quickly abate when the clamp is released. He also found that when normal saline was substituted for drinking-water in these animals sudden generalised œdema sometimes developed, the onset of the cerebral attack being accelerated by this procedure.

The experimental production of salt and water retention, hypertension, albuminuria, and fits in animals by renal ischæmia (albeit unilateral) must strikingly compare with the clinical signs of pre-eclampsia/eclampsia. The uterorenal reflex can visually provoke bilateral renal ischæmia,[6] and it has been shown to reduce the renal plasma-flow by 25% [7]—both in animals. Clinically, conditions causing the myometrium to resist stretch have been shown to underlie the toxæmic state [6] and much evidence has accumulated that there is a reduction in renal hæmodynamic values and cerebral circulation in severe pre-eclampsia. Further, the exhibition of renal vasodilator drugs—e.g., apresoline—have proved of infinite value in the control of the pre-eclamptic state, thus emphasising the underlying renal ischæmia.

That resistance of the uterus to stretch has been clinically recognised in the ætiology is evident in the treatment practised by Krishna Menon [8] who has stressed the immense and unmistakable value of rupture of the membranes in the urgent treatment of toxæmia. One recent and very important finding is that of Reynolds [9] which helps strongly to support my ætiological thesis. These authors have shown that *the tension in the uterus mounts when the uteroplacental circulation is obstructed* either by active or passive engorgement of the placenta. Hereby the infarcted large or hydatidiform placenta can be included in the ætiological thesis of resistance to uterine stretch.

It becomes evident on all sides that impartial assessment of worthwhile data confirms the correctness of the uterorenal ætiology of toxæmia.

Worthing. JOHN SOPHIAN.

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2. Howard, J. E., Berthrong, M., Gould, M., Yendt, E. R. *Bull. Johns Hopk. Hosp.* 1954, **94**, 51.
3. Shackman, R., Graber, I. G. *Brit. med. J.* 1956, i, 1321.
4. Fajers, C. M. *Acta path. microbiol. scand.* 1955, suppl. 106.
5. Byrom, F. B. *Lancet*, 1954, ii, 201.
6. Sophian, J. Toxæmias of Pregnancy, London, 1953. See also *Excerpta Med.* 1958, sec. x, **11**.
7. McGaughey, H. S., Weller, H., Anslow, W. P. *Amer. J. Obstet. Gynec.* 1956, **72**, 589.
8. Krishna Menon. Lecture at University College Hospital, London, May 31, 1960.

PROGNOSIS FOR ALCOHOLICS

SIR,—Allow me to add some information to your note (May 7) about my article [10] which Dr. Glatt commented on (June 4). Abuse before the age of 21 correlated −0·25 with the follow-up result, no abuse before the age of 30 correlated +0·18, age over 40 in itself +0·11, more than five arrests for drunkenness −0·25. An important feature of the treatment plan was the appointment in each case of a "trustee" (wife, mother, employer, &c.), who dispensed the tablets and reported weekly to the supervisor.

Socialnämnden, Skånegatan 26,
Gothenburg, Sweden. C.-G. BERGLIN.

A NEW DIAGNOSTIC TEST IN AMYLOIDOSIS

SIR,—May I comment on the preliminary communication by Dr. Jarnum in your issue of May 7? He is undoubtedly correct in assuming that Evans-blue is taken up by amyloid tissue, but this observation is certainly not original and was mentioned by Unger et al.[11] as far back as 1947. Furthermore, these authors noted that at necropsy much of the Evans-blue had been absorbed by any amyloid tissue present in the body.

Before any of the tests described by Dr. Jarnun start being widely used, I would like to draw attention to some not too obvious fallacies. In the first procedure he describes, it is recommended that blood samples are taken at 4 and 15 minutes after the injection of a known quantity of Evans-blue. The dye content of each sample is then compared, and if the second specimen contains 80% or less dye than the 4-minutes specimen, Dr. Jarnum feels that amyloidosis is probable. It is assumed in this procedure, first, that mixing of the dye is complete in 4 minutes, and, second, that no significant amount of dye is absorbed in this period. Neither of these assumptions is correct.[11 12] It can be shown very simply that mixing is incomplete till 8 to 10 minutes after injection by giving intravenously a small dose of human serum-albumin tagged with ^{131}I (I.H.S.A.) and then taking blood samples at 2-minute intervals for the next 14–16 minutes. Each sample is counted and it is found that constant counts occur only after 8–10 minutes. If congestive failure is present, mixing may be delayed for 20–25 minutes after injection.

The second procedure assumes that the binding capacity of serum for Evans-blue is always the same in the absence of amyloidosis. In practice the binding capacity of serum for vital dyes and hence the rate of loss of dye from serum probably depends not only on the level of serum-albumin but on other protein constituents of the serum.[13] It would seem that Evans-blue is a useful agent for measuring plasma-volumes only when there is no dysproteinæmia in the subject being investigated.

University of Maryland
School of Medicine, Baltimore. W. K. C. MORGAN.

9. Reynolds, S. R. N., Bienar, I. Z. J. (in the press). Quoted by Ramsay, E. M. *Amer. J. Obstet. Gynec.* 1959, **77**, 1016.
10. *Svenska Läkartidn.* March 11, 1960, p. 801.
11. Unger, P. N., et al. *J. clin. Invest.* 1947, **27**, 111.
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13. Larsen, B. *Ann. rheum. Dis.* 1958, **13**, 211.

"SPIRITUAL HEALERS" IN HOSPITAL

SIR,—Mr. Harry Edwards (June 11) assumes that Dr. Cotton Cornwall has presented the strongest case against the new practice of allowing "spiritual healers" to attend the sick in hospitals. I would like to record an experience of mine in this connection.

I was invited to attend a demonstration of spiritual healing given by Mr. Edwards in the St. Andrew's Hall, Norwich, on Nov. 12, 1949.

He began by saying that any healing that they might see would not take place through any physical skill of his or his helpers. A number of patients were brought on to the platform; one of them being a little girl with poliomyelitis affecting one leg, who happened to be a patient of mine. She was lifted on to the platform and into a chair and was wearing a short iron, to support a flail foot, which had been ordered by me. The healer approached the child and ordered removal of the iron and then took the child by the hand and said "get up and walk", which she did to the astonishment of everybody. Of course, they did not know that the child could walk like that beforehand, but I did. There were even cries of "it's a miracle". I saw the same child the next week at my clinic at the Children's Hospital; there was no change whatever in her condition and fortunately the mother had replaced the short iron.

There were other cases "healed" at the same time. I remember one of them quite well—a man with a stiff shoulder, which was quite vigorously manipulated in direct contrast to the opening words of the healer. The patients were subjected to suggestive treatment and were encouraged to do their best in front of a large audience, and there was also a certain amount of handling and manipulations—all well-recognised methods of treatment, but not spiritual healing.

I would like to say that I am a firm believer in cooperation between medicine and the Church. But these experiences of mine put "spiritual healing" as demonstrated in Norwich in November, 1949, at quite a different level. If benighted patients want this form of treatment let them go and have it at the spiritual healer's home or centre, but not in the recognised hospitals of this country.

Norwich. G. K. MCKEE.

FATTY FOODS AND OBESITY

SIR,—In their letter of May 28, Professor Kekwick and Mr. Pawan repeat their claim that a decrease in body constituents other than water (i.e., fat) is involved in the weight-loss produced over a short period by a fatty diet; in other words, that such a diet brings about an increased tissue catabolism. If Kekwick and Pawan were right in this contention, it should be easy to demonstrate, during the high-fat period, the increase in energy expenditure which must necessarily accompany the accelerated combustion of fat. However, present evidence, including our experiment, is against any significant increase in metabolic-rate on a high-fat regimen; if more fat is burnt on the unaltered oxygen consumption recorded by us, it has to be at the expense of other fuel, probably carbohydrate, and this would even indicate a reduced energy utilisation, considering that 1 litre of oxygen used for burning fat yields fewer calories than 1 litre used for combustion of carbohydrate (about 4·7 and 5·0 kCal., respectively).

Kekwick and Pawan's demonstration of a fat-mobilising factor released on a high-fat regimen is most interesting, but does not exempt us from observing the law of constant energy: the fact that more fat is mobilised might be expected to result in hyperlipæmia, but it does not per se indicate that more fat is burnt.

The increase in insensible water loss which Kekwick and Pawan have found in patients on a fatty diet is no reliable indicator of a corresponding increase of the metabolic-rate; thus Passmore, Strong, and Ritchie [1] found that evaporative water-loss varied considerably although calorie expenditure and diet remained unaltered.

Nor should we be too much impressed by the fact, also referred to by Kekwick and Pawan, that high-fat feeding inhibits the in-vitro lipogenesis in adipose tissue from rats [2]—in view of the observation that rats do actually grow fat on high-fat diets.[3]

Until the disappearance of fat is properly accounted for, we feel justified in "falling back on to the old argument": that a change in total body-water is the major reason for the changes occurring in body-weight when shifting between equicaloric diets rich in either fat or carbohydrate. In our support we may cite Benedict and Milner [4] who demonstrated a large negative water balance on a high-fat diet and, conversely, a positive balance on a high-carbohydrate diet. Also Passmore et al.[1] found a positive water balance in two persons receiving 1000 calories with 90% carbohydrate.

7th Department of Medicine, Kommunehospitalet, Copenhagen. E. S. OLESEN F. QUAADE.

HEPATITIS AFTER INOCULATIONS

SIR,—Twenty years ago the late Sir Alexander Fleming used to demonstrate a method of sterilising a single syringe and needle for use during mass inoculations. Medicinal paraffin heated over a flame to about 150°C was sucked in and out of the syringe, with the needle in situ, between each injection. I have never used this simple method myself, but I am surprised that no-one from St. Mary's has written to you about it.

London, N.W.1. JOHN BRAY.

LATEX AGGLUTINATION REACTION IN NON-RHEUMATIC DISEASES

SIR,—In your annotation of March 26 and in Dr. Morgan's letter of April 9, the topic of latex agglutination reaction in non-rheumatic diseases was discussed. You correctly underscored Dresner's findings [5] as emphasising a basic difference between the factors responsible for agglutination of globulin-coated latex particles and the agglutination of erythrocytes sensitised with "amboceptor".

Recent studies of Epstein et al.,[6] Lospalluto and Ziff,[7] and Franklin [8] have clearly demonstrated that there are at least two rheumatoid factors. One of these reacts with rabbit gamma-globulin, the other with human gamma-globulin. Those observations should be taken into consideration when interpreting discrepancies between latex fixation tests and "amboceptor"—sensitised erythrocyte procedures. The latex (polystryene) particles are coated with human gamma-globulin, whereas the red cells used for the Rose-Waaler D.A.T. were coated with rabbit antibody gamma-globulin (amboceptor).

In our own laboratory [9] we have found that alligator erythrocytes lend themselves to detection of rheumatoid factor(s) by direct or inhibition hæmagglutination procedures. We have observed that 6 of 44 subjects with liver disease due to carcinomatosis or cirrhosis were positive by alligator hæmagglutination. By slide latex fixation, 7 were positive. Whereas

1. Passmore, R., Strong, J. A., Ritchie, F. J. *Brit. J. Nutr.* 1959, **13**, 17.
2. Mâsek, J., Fábry, P. *Experientia, Basle*, 1959, **15**, 444.
3. Hausberger, F. X., Milstein, S. W. *J. biol. Chem.* 1955, **214**, 483.
4. Benedict, F. G., Milner, R. D. Experiments on the metabolism of matter and energy in the human body, 1903–1904. Bull. 175. U.S. Department of Agriculture. Office of Experiment Stations, 1907.
5. Dresner, E., Trombly, P., O'Brien, G. F. *New Engl. J. Med.* 1959, **261**, 981.
6. Epstein, W., Johnson, A. M., Rogan, C. *Proc. Soc. exp. Biol. Med.* 1956, **91**, 235.
7. Lospalluto, J., Ziff, M. *J. exp. Med.* 1959, **110**, 169.
8. Franklin, E. G. *Arth. Rheum.* 1960, **3**, 16.
9. Cohen, E., Neter, E., Mink, I., Norcross, B. M. *Arch. Inter-Am. Rheum.* 1959, **2**, 75.

cold precipitates and euglobulin fractions of serum of rheumatoid arthritis patients showed agglutinating activity, the precipitates and globulin fractions of sera of patients with non-rheumatoid diseases were often negative, although the whole sera themselves, were actively positive.[10] Sera of subjects with syphilis or of healthy blood-donors have been consistently negative. However, Bloomfield[11] has reported positive latex fixation by sera of patients with syphilis. By concurrent use of hæmagglutination, latex fixation and serum fractionation, the agglutination reactions of some non-rheumatoid sera were distinguishable from those of rheumatoid sera.

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K. SHIMAOKA
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Division of Medicine,
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SKELETON IN THE LINEN CUPBOARD

SIR,—The role of blankets in cross-infection is well established, and there has been considerable research into techniques designed to reduce their bacterial content. Unfortunately little thought has been devoted to an equally relevant problem—namely, the maintenance of bacteriological cleanliness in the period between laundering and subsequent use. The importance of this latter factor was realised after a study on bed-linen and blankets carried out after an outbreak of surgical sepsis in which blankets were implicated.

It was established that blankets could be rendered relatively and adequately sterile by the method of Blowers and Wallace.[12] It was also found that significant reinfection was occurring during transport and storage.

The procedure then in use was to return freshly laundered bedding to the wards in canvas bags. These bags were also used to convey used bedding from the wards to the laundry, but they were washed before being used for clean bedding. In the wards the linen and blankets were stored, uncovered, on bare shelves in the linen cupboards. It was noted that no attempt was made to store the bedding in a last-in last-out rotation. It was also customary to store in the cupboard, alongside the freshly laundered material, blankets which had short use in the wards.

As a result the linen cupboard contained an assortment of bacteriologically clean and dirty bedding, and tests showed that any blankets not used immediately after laundering soon acquired a heavy bacterial content.

To reduce the hazard of contamination of the blankets during transit and storage a trial was made of packing the blankets in groups of four in a strong polyethylene bag immediately after washing. From a bacteriological standpoint this was extremely satisfactory. No change in the low or absent bacterial count could be found after prolonged storage or removal of two or three blankets from the bag. Economically, however, the method proved disappointing. The cost of each polyethylene bag was 5*s*. and there was, for a variety of reasons, a very high wastage during use.

To overcome this difficulty a trial was made using 'Cellophane' sheet instead of the polyethylene bags. This proved economically and bacteriologically satisfactory, but due to careless handling during transit the majority of packs arrived in the wards with the cellophane torn. This problem was finally overcome by packing the cellophane-wrapped blankets, three per pack, in a strong fibre case. This method of transport has proved very satisfactory and few, if any, tears have arisen since it was introduced. On arrival in the ward the cellophane packs are stored in the linen cupboards, care being taken not to damage the cellophane. Tests have shown that the wrapped blankets have remained bacteriologically clean over periods as long as 12 weeks.

In order to prevent any ward organisms being introduced into the linen cupboard a complete ban has been placed on the use of the cupboard for storing bedding from the ward. This one-way traffic, laundry/linen cupboard/ward, has been combined with an overhaul of bedding hygiene.

Every patient on admission is put in a bed which is made up with freshly laundered bedding, and under no circumstances are any blankets to be put on an adjacent bed, even though it is unoccupied.

After discharge of a patient both blankets and linen are to be returned to the laundry for washing.

If a blanket is required for a patient during transport to another department a freshly laundered one is used. If it is frequently required then it is stored in the patient's locker and must not be put back in the linen cupboard.

Unoccupied beds, as far as possible, are not made up until shortly before a patient's admission, though one or two can be kept ready for emergencies. Infected cases must obviously have frequent changes of all bedding. All bedding is stored on a last-in last-out basis.

It is obvious that if measures are to be taken to produce bacteriologically satisfactory bedding then subsequent handling must be such as not to prejudice the efforts involved.

Cotton and linen goods are boiled during washing and have a greater turnover. They have not been found to acquire any resident bacterial flora during storage and are therefore still delivered in canvas bags. Blankets, however, do appear to acquire bacteria with greater ease, and the method of cellophane-pack/fibre-bag delivery has proved very satisfactory over the past eighteen months. The extra cost is insignificant in comparison with the total work undertaken.

In spite of the more frequent washing that blankets now receive the number of new blankets required has not shown any increase.

These rules adopted for linen-cupboard and bedding hygiene are all simple and obvious, and no cases of cross-infection have occurred since their introduction. The overall rate of sepsis is appreciably less; infected wounds have shown an increase in the speed of healing; and one noticeable result has been a higher percentage take of skin grafts.

It is suggested that the ward linen cupboard is worthy of a great deal more attention from the hospital medical staff than is normally given to it. At the same time the system of delivery of bedding and its subsequent handling in wards must be considered, for we have little doubt that the majority of linen cupboards will be found to contain a very small but highly ubiquitous skeleton.

I. MCGILVRAY
M. H. HALL.

Whiston Hospital,
Prescot, Lancs.

SNAKEBITE

SIR,—The word "envenomation," questioned by Dr. Penman (April 2), although omitted by *The Shorter Oxford English Dictionary*, *is* to be found in *Webster's New International Dictionary of the English Language*[1] (p. 855) as follows:

(*a*) "Envenom. 1. To poison as by a venomous bite. Envenomation, n."

"Envenomation" is more specific than "poisoning" when venom is the noxious agent. Since the mildly poisonous *Vipera berus* is the only venom-bearing snake to be found in the British Isles and, according to the records of the past 70 years, fatalities from the bite have been extremely rare, it is understandable that the word "envenomation" should have found little use. On the other hand, many highly dangerous species are indigenous to the United States; hence the need of a more specific term than "poisoning."

ELEANOR E. BUCKLEY.

Wyeth Laboratories,
Philadelphia.

10. Cohen, E., Shimaoka, K., Hermes, P. *Proc. N.Y. Ass. publ. Hlth Lab.* 1960 (in the press).
11. Bloomfield, N. *J. Lab. clin. Med.* 1960, **55**, 73.
12. Blowers, R., Wallace, K. R. *Lancet*, 1955, i, 1250.

1. 2nd ed. Springfield, Mass., 1944.

Obituary

HENRY LETHEBY TIDY

K.B.E., M.A., D.M. Oxon., LL.D. Belf., F.R.C.P.

Sir Henry Tidy's work as a physician was centred on St. Thomas's Hospital and Harley Street; but through his writings, his travels, and his service with the Army he was known and admired by many colleagues outside London and outside this country. He died, as we announced last week, on June 3 at the age of 82.

He was the only son of Charles Meymott Tidy, who for many years held the chair of chemistry, medical jurisprudence, and public health at the London Hospital, and nearly a century later he used to recall his father's comments on the consultants of the 'seventies and 'eighties. He was educated at Winchester, New College, Oxford, and the London Hospital. He qualified in 1906 and held resident appointments and a registrarship at the London Hospital before spending some time abroad in the clinics of Freiburg and Berlin. On his return he set up in consultant practice in Harley Street. His first appointments were at Poplar Hospital and the Royal Northern Hospital, but in due course he was elected to the staff of St. Thomas's Hospital, and for many years he was also dean of the medical school.

Elliott & Fry

Tidy's wide clinical experience, exhaustive reading, and talent for lucid and orderly exposition were clearly seen in his *Synopsis of Medicine*, which first appeared in 1920. Its success was confirmed in subsequent editions, and the tenth was reached in 1954. He was also for many years one of the editors of the *Medical Annual*. His own research was based on clinical percipience reinforced by laboratory investigation—he was a fellow of the Chemical Society, and his early posts included that of clinical pathologist at The London. His first papers dealt with gastric contents and leukæmia, and in 1919 he investigated an epidemic due to *B. aertrycke* for the then Medical Research Committee. But he will perhaps be chiefly remembered for his studies on glandular fever, which in the early 'twenties was prevalent in this country. Thanks to this experience he was quick to draw attention to the epidemic which broke out in 1930. His Lumleian lectures to the Royal College of Physicians in 1934 were a valuable and exhaustive review of this protean disease.

Tidy also served the college in many offices besides that of Lumleian lecturer. He had been elected to the fellowship in 1919, and he was successively elected examiner, councillor, censor, representative on the General Medical Council, and registrar. Other medical bodies in which he took a prominent part included the Royal Society of Medicine, the Association of Physicians of Great Britain, and the British Society of Gastroenterology, over all of which he at one time presided.

He also had a long association with the Army Medical Services. During the 1914–18 war he had served as a major in the R.A.M.C., and he was honorary consultant physician to the Army at the Queen Alexandra Military Hospital, Millbank, for some years before the late war. In 1939 he accepted the appointment of consulting physician to the Army at the War Office, and of this strenuous part of his career A. G. B. writes:

"With his previous knowledge of military medical requirements Tidy was well qualified to advise the director-general, and all who worked with him found his quiet manner in dealing with difficult problems helpful not only to the specialist medical officer but also to the administrative medical staff. He took a special interest in the regimental medical officers and when visiting commands always made a point of seeing them and helping them with their problems."

Tidy reached the rank of major-general and was knighted in 1943. He also received awards from the Governments of the United States, Holland, Belgium, and Czechoslovakia.

After his retirement from St. Thomas's his interests were widened by his appointment as a visiting professor to the University of Cairo. From 1946 to 1951 he spent each winter in Egypt, and of these visits W. R. B. writes:

"Harry Tidy's outstanding qualities—commonsense, thoroughness, perseverance, and kindness—though not, perhaps, exceptional ones—made him in his way an exceptional man. The capacity to extract the essentials of a subject or situation was the basis alike of his best-selling textbook, and his clinical acumen; and his commonsense and friendliness soon established him as a British institution in Egypt—a kind of British pasha in the days when there were still pashas. From Christmas to Easter he regularly taught in the Medical School, and practised in Cairo to the great advantage of Egyptian medicine; and Anglo-Egyptian understanding was fostered by the lasting friendships he and Lady Tidy formed with the leading Egyptian doctors and their families. Their zest for new scenes was unabated by age and they recently sailed round the world, paid a visit to the Persian Gulf, and were hoping to go to British Guiana".

From 1929, when he was appointed a visitor, Tidy had shared in the work of King Edward's Hospital Fund. He served on the hospital economy committee in the 'thirties, and was appointed to the general council in 1936. But from the end of the war to within a few months of his death he gave it a great part of his time. He served on the distribution and management committees, the committee of the Hospital Administrative Staff College, and on all his firm character and good sense gave weight to his opinions. But perhaps his chief interest lay in the convalescent homes committee which he started from nothing in 1946. R. E. P. recalls:

"When Sir Henry started he knew little or nothing about convalescent homes—or so he said. These were not famous places like St. Thomas's or The London where his roots lay, but he set about learning about them with diligence and by constant visiting. His wise and kindly approach to the problems of those small homes won him many friends so that his visits were happily awaited—much more for the pleasure of meeting him than for the possible financial benefits. Nevertheless, the financial side was important and he could act with speed. One July day he found a home's milk supply hidden under the front-door step to keep it cool. At once he said: 'Go and buy a refrigerator today and I will get a grant for it later.' He had a warm place in his heart for those who worked for the good of others without thought of profit or reward and many a chairman or matron of a modest home will regret the loss of a friend".

R. C. J. adds this personal tribute:

"Henry Tidy, notwithstanding his very remarkable professional achievements was a modest, rather retiring type of man. He never threw his weight about. When we were at Oxford together he showed considerable athletic skill and was no mean performer in running and boxing. He was president of the St. Thomas's Athletic Club in which he always took great interest. For the greater part of his life he devoted himself to his work and except for occasional golf and fishing allowed himself little in the way of recreation. He possessed

a very sound judgment, his wise counsel was much valued by the many committees on which he served. He was a true friend and a loyal colleague. Tidy had a quiet sense of humour and this, with his kindly and gentle manner, gained him a large number of friends who will long remember him".

Sir Henry married in 1906 Elizabeth Catherine, daughter of the late Sir William Ramsay, and she survives him with two sons and a daughter.

CHARLES SINGER

M.A., D.M., D.Litt., Hon. D.Sc. Oxon., F.R.C.P.

Dr. Charles Singer, emeritus professor of the history of medicine in the University of London at University College, died on June 10 at his home in Cornwall.

The son of the Rev. Simeon Singer, a Hebrew scholar of distinction, he was born in London on Nov. 2, 1876. He was educated at the City of London School and at University College, London. In 1896 he became a scholar of Magdalen College, Oxford, of which he was afterwards an honorary fellow. At Oxford he read zoology; but medicine was his aim, and he went on to St. Mary's Hospital for his clinical training. In 1903 he took the conjoint qualification, and straightway went, as medical officer, on an expedition under Sir John Harrington for the delimitation of the Abyssinian frontier with the Sudan. On his return he held resident posts at St. Mary's and other hospitals, and gained further experience in tropical diseases in a post in the Government General Hospital at Singapore. In 1909 he began consulting practice and was appointed physician to the Dreadnought Hospital for Seamen. He was also medical registrar to the Cancer Hospital, Brompton, and there made a study (with S. B. Schryver) of the chemical composition of the gastric juice in carcinoma and other diseases. But he had already found time to write several papers on medical history and begin work *On the Development of the contagium vivum*, 1500–1750. In 1914 he gave up consulting medicine, and on Osler's invitation went to Oxford to start his life-work as a medical historian. He and his wife, who shared his interests, set up a history of science room in the Radcliffe Camera.

When the war came, Singer took a commission in the R.A.M.C. He was first posted to Malta. While there he began some anthropological and archæological work with Sir Themistocles Zammit. In 1916 he was transferred to Salonika and pursued his studies in Byzantine and modern Greek. Such was his zeal and enthusiasm that Osler termed him "that Socratic gadfly". With his wife's help, through correspondence, Singer was able to publish the first volume of his studies in the *History and Methods of Science*. After the war he returned to Oxford as lecturer in the history of the biological sciences. In 1920 he was appointed lecturer in the history of medicine at University College, London, and in 1931 he was elected to the chair which he held till his retirement in 1942.

Singer knew many languages. He could read ancient and modern Greek, Latin, Arabic, Anglo-Saxon, French, German, Dutch, Italian, and Spanish. This acquaintance with ancient and modern tongues was a great help in his work. Among his chief works were *Greek Biology* and *Greek Medicine* (1922), *History of the Circulation of the Blood* (1922), *A Short History of Medicine* (1928), *Historical Relations of Religion and Science* (1928), *A Short History of Biology* (1931), and *A Short History of Science* (1941). He was one of the editors of the four volumes of the *History of Technology* (1954–58).

He was president of the third International Congress of the History of Medicine (1922) and of the second International Congress of the History of Science and Technology (1931). He gave the FitzPatrick lectures to the Royal College of Physicians on the evolution of anatomy in 1923–24. He was Noguchi lecturer at Johns Hopkins University and Mary Scott Newbold lecturer at Philadelphia in 1930. During 1931–32 he was visiting professor at the University of California. He was elected F.R.C.P. in 1917. He was also Fellow of the Society of Antiquaries, an honorary fellow of the Royal Society of Medicine, and a fellow of University College, London. He was a past president of the British Society for the History of Science, and the International Society for the History of Science. He held the Oxford doctorates in the faculties of medicine, letters, and science, the D.SC. being an honorary degree. The *Festschrift* presented to him in 1953 contained a detailed bibliography of his own writings, and 90 essays contributed by leading historians in Great Britain, the United States, and the Continent, which ranged from the twilight of history to the 19th century and after. This work was later published as *Medicine, Science and History*.

A. MACN. writes:

"Charles Singer founded a school of historical research in medicine and science, illuminated it with scholarship, thought, and wisdom, and gave forth its lessons with eloquence and literary distinction. He had a delightful personality. He was kind and generous, scintillated with ideas for the improvement of mankind, and, as his work before and during the late war showed, was a friend to the oppressed. He helped to found the Society for the Protection of Science and Learning, and he and his wife rescued and succoured many victims of Nazi tyranny. He was ever ready to pour out the stores of his knowledge to help the budding historian and others on the ladder of life. His conversation was adorned with wit and humour, and he and Mrs. Singer were delighted to entertain their friends—and of these there were many—at Kilmarth or in London. The world is the poorer for Charles Singer's passing, but his works abide with us."

Professor Singer married in 1910 Dorothea Waley, daughter of Nathaniel L. Cohen, who has won an international reputation as a medical historian in her own right.

Prof. ESTHER KILLICK

M. F. L. K. writes:

"The untimely death of Esther Killick will be deeply felt, not only by members of the Royal Free Hospital School of Medicine and the University of London, but also in far wider spheres. She was a woman of outstanding character and ability. She had powers of leadership and analysis and also possessed great courage, calmness of judgment, and a precision of thought clear-cut as her admirable profile. Endowed with these gifts she made a superb chairman or committee member, and as such she gave unstinting help to the Royal Free Hospital School of Medicine, the University of London, and many outside bodies. Her habitual appearance was one of stillness and reserve which gave a false impression of aloofness, because those who really came in contact with her soon realised her friendliness, and those who sought her help and advice invariably found her a willing listener and a kindly mentor. Moreover she and her husband, Prof. St. John Huggett, and their children enjoyed an extremely serene and happy home life, which surely was the basis of her tranquillity."

Appointments

BAIN, A. D., M.D. Edin.: consultant pathologist, regional pædiatric pathology service, Royal Hospital for Sick Children, Edinburgh.

COOK, I. A., M.D. Aberd.: consultant pathologist (hæmatologist) in charge, hæmatology department, and director of regional blood-transfusion service, Royal Northern Infirmary, Inverness.

JONES, W. W., M.B. Belf., F.F.A. R.C.S., D.A.: consultant anæsthetist, Glasgow Royal Infirmary.

MCINTOSH, A. D., M.B. Edin., M.R.C.O.G.: consultant gynæcologist and obstetrician, Lanarkshire maternity service.

MOSS, B. J. L., M.B. Lond., D.C.H., D.P.H.: M.O.H., Leicester.

RICHMOND, H. G., M.D. Aberd.: consultant pathologist in charge, pathology department, Royal Northern Infirmary, Inverness.

WILSON, P. R., L.R.C.P.I.: school M.O., Cornwall.

The Hospital for Sick Children, Great Ormond Street, London:

FORBES, C. E., M.D., B.SC.: house-physician.

MCKAY, S. R., M.B. Melb., D.T.M. & H.: house-physician.

PARRY, G. R., M.B. Lond., F.R.C.S.: surgical outpatient assistant.

RENWICK, A. G. C., M.B. Edin.: registrar, department of chemical pathology.

Notes and News

EMPHYSEMA AND BRONCHIOLITIS

SPEAKING to the Manchester Medical Society's section of pathology on May 25, Prof. J. Gough said that morbid-anatomical changes are much more clearly seen in lungs if these are fixed in expansion before they are cut. This applies especially to certain forms of emphysema. Centrilobular emphysema, for instance, is not always easy to identify at necropsy, but is clearly seen in the expanded lungs, especially if thin slices are examined. The existence of this type of emphysema as a common finding has been confirmed in several places in Britain, and also in Australia and the United States. It is due to bronchiolitis, but further studies are required to show whether this is always infective or may be caused by other agents from the atmosphere. Thin sections of expanded lung show clearly the difference in the effects of spasmodic asthma and of chronic bronchiolitis. In asthma the lungs are over-distended but usually there is no destructive emphysema, whereas with bronchiolitis the destructive centrilobular type is characteristic. The airway obstruction of byssinosis is associated with changes indistinguishable from ordinary bronchitis, the accompanying emphysema being of destructive type.

An observation of fundamental importance is that of Caplan who found distinctive radiological changes in the lungs of rheumatoid coal miners. The pathological changes which underlie the radiological ones are also distinctive and show a combination of rheumatoid and pneumoconiotic lesions. The interpretation of how certain dusts, especially coal dust, can render the lung vulnerable to the rheumatoid change seems a field for fruitful research.

A condition which appears to be a new disease is Alveolar Proteinosis. Among the 27 cases which comprised the first report in 1958 only one came from Britain, but since that time other cases have been identified in this country. The condition is easily confused with pneumocystis carinii pneumonia, both in its radiology and its gross morbid anatomy. The lesions, however, can usually be distinguished histologically without difficulty.

OLD PEOPLE: AN ESSAY IN COORDINATION

IT is almost a truism to say that the medical care of old people involves much beyond " medicines ", and that one of the greatest difficulties is in coordinating the many authorities and existing facilities. At Sunderland General Hospital the department of medicine and geriatric medicine is to investigate the effect of combining some of these through a day hospital. To this will be brought a random sample from five hundred former inpatients who are known to have been living alone after their discharge from hospital. They are classified according to sex, and according to age (60–75, and over 75), and will be gathered from five districts—one for each day. The effect of such a weekly visit to this special part of the department will be assessed by independent observers at intervals during the first eighteen months.

The accommodation set aside has facilities for medical examination, ablution, chiropody, physiotherapy, occupational therapy, assistance from the almoner and from welfare officers, and meals during the day—for 1*s.* 6*d.* The local authority provides transport through the ambulance service, and the hospital provides medical, physiotherapeutic, and feeding services. The hospital's league of friends helps with administration and with many of the extra services and comforts which will be needed. All patients are seen in their homes by a health visitor and a doctor before the investigation and at three-monthly intervals.

A grant from the scientific and research subcommittee of the Newcastle Regional Hospital Board covers the salary of a clerk, and contributes to preparation of the accommodation; but a great deal of the effort, and much economy in the cost, come from voluntary sources. Apart from the undoubted benefit to these deserving patients, the investigation is an attempt to see whether the local health authority, the hospital service, the related branch of the Civil Service, and the voluntary organisations can be brought together to achieve a single purpose.

COST OF BECOMING A DOCTOR

IN the United States, when the public complain (as they often do) about the high fees their doctors charge, the doctors point with some justification to the amount of cash (as well as hard study, responsibility, and so on) that their medical education has cost them; for, though the fees paid by students contribute only a minor fraction of the cost of running a medical school, those fees are much higher than the fees usual in Britain; moreover, they come after the similarly high fees paid for tuition at college, since two to four years' premedical college education is generally required.

Some figures about this high cost of medical education, and its consequences, have been published by the Association of American Medical Colleges.[1] The average cost of his four years' professional training to the 1959 graduate was $11,642. Many students obtain loans, and 81% hold outside jobs, often unconnected with their medical education; but financial help from families remains a big factor. Only 16% of students had no such help, and over 80% of all the costs were defrayed by families. This makes it inevitable that the medical schools have a high proportion of students from the wealthier families; thus the 11% of American families with an income of over $10,000 a year provided 43% of the medical students, and nearly half came from the median income-group with incomes of $5000–10,000.

COLOUR TELEVISION DEMONSTRATION

A GROUP of lectures on Cell, Chromosome, and Virus Microscopy in Cancer Research, devised and coordinated by Prof. A. Haddow and Prof. G. J. Cunningham, was presented at the Royal College of Surgeons of England by means of large-screen colour television on May 10.

Dr. E. M. F. Roe, speaking from a distant studio, discussed photomicrographs of living cells taken with a normal microscope and phase-contrast, dark-ground, and fluorescence techniques. Dr. E. J. Ambrose showed normal and malignant kidney cells by interference microscopy and suggested that the apparent lack of adhesion between the cell membranes of the latter might be responsible for the spread of cancer. Professor Cunningham demonstrated the technique for rapidly freezing cells to what he called the " nearly living " state. Showing that there was an unusual deposition of fat in certain basal cells associated with abnormal tissues in normal bronchi, Professor Cunningham suggested that fat-soluble carcinogens might dissolve in this fat and initiate cancer.

Dealing with the role of chromosomes, Prof. P. C. Koller introduced a film which was projected in the lecture-hall. He explained that the mitosis shown in the film could be arrested in the metaphase stage and the variations from the normal number of chromosomes associated with certain tumours could be analysed. Dr. S. H. Revell demonstrated the effect of radiation on chromosomes and showed how micronuclei were formed by the abnormal division of the chromosomes. Finally, Dr. R. J. C. Harris discussed the role of the virus in cancer. A virus grown on the embryo cells of a mouse can cause widespread cancer in hamsters and other animals.

The excessive heat from the intense light caused considerable strain. Is this wholly unavoidable? Why should a lecturer be separated from his audience by a couple of miles when it would be to their mutual advantage to be in the same hall? This is not to decry the usefulness of television: the many demonstrations involving laboratory facilities and live animals to illustrate the lectures needed enlargement on the screen to be seen clearly by the huge audience. But television, like the lantern-slide and film, is but a visual aid; and when the novelty is over, it will doubtless take its place with them.

CONTRIBUTION OF SURGERY TO CLINICAL CARDIOLOGY

THE lecture that Mr. T. Holmes Sellors gave in Edinburgh last year is now obtainable from the publications department of the Royal College of Physicians, 9, Queen Street, Edinburgh 2 (4*s.*, postage 6*d.*). It was the George Alexander Gibson

1. *New York Times*, May 29.

lecture of the college, and it concludes by saying that Dr. Gibson, had he lived a few more years, "would have been able to see his observations and deductions proven at operation . . ." One of the best contributions that surgery can offer the clinical cardiologist, Mr. Sellors points out, "is the opportunity of seeing the pathological heart exactly as it is in the body".

University of Oxford

On June 4 the following degrees were conferred:

D.M.—C. J. Dickinson, H. C. Nohl.
B.M.—Robert Cook.

University of Cambridge

Dr. L. G. Whitby has been appointed university biochemist to Addenbrooke's Hospital.

University of London

Dr. A. J. Buller, senior lecturer in physiology at St. Thomas's Hospital Medical School, has been appointed to the readership in physiology at King's College, and Mr. D. F. N. Harrison, senior registrar to the ear, nose, and throat department at Guy's Hospital, to the readership in laryngology at the Institute of Laryngology.

Royal College of Surgeons of England

At a meeting of the council on June 8, with Sir James Paterson Ross, the president, in the chair, Prof. Carl Semb (Oslo) was admitted to the honorary fellowship. Diplomas of fellowship were granted to the following:

T. E. Jeffreys, R. T. B. Jones, Delia M. H. Cothay, J. L. Somervell, J. R. F. Ingall, J. M. Dolphin, J. R. Kirkup, *C. G. Keith, J. H. H. Webster, P. C. Anderson, L. J. Lawson, D. W. Atkinson, Malcolm Swann, P. R. Hawley, M. A. Nelson, H. C. Smith, Ratan Lal Agarwal, J. W. Eadie, D. M. Davies, D. M. Boyd, J. N. Cozens-Hardy, J. D. Sheils, Mohomed Nafick Burhan, *T. D. H. Gray, †J. A. O'Reilly, Thethravusamy Joseph Aloysius, John Considine, F. J. Ensell, M. R. Mynhardt, Benarsi Lal Talwar, *Jagdish Sarup Gupta, K. L. Hayes, †K. T. Jones, A. D. Lyall, Rajendra Nath Mullick, C. V. Petersen, †Shrof Ramasetty Chandrasekha, I. A. Le G. Ferguson, R. L. Garner, J. N. Gibson, M. C. T. Morrison, Suniti Ratnakar Samsi, G. A. G. Scarlett, Prakash Chandra Bansal, A. P. Blower, B. W. Broadhurst, D. G. Calvert, *J. F. Cullen, Amal Kanti Dharbhaumik, I. S. Lister, Pradip Mazumder, Mookkassanairveettil Pullare Achutha Menon, P. J. Molloy, Sein Myint, E. P. Simkin, Donald Solomons, G. W. Sprigge, R. D. Upton, *B. J. Bowden, E. R. Briant, G. R. Duncan, Muttukuttige Bernard Clement Perera Gunawardene, J. E. Handelsman, Labib Naiem Hasso, J. D. Iswariah, D. R. Kennedy, R. J. Kitchin, Jacob Thannikal Kuruvila, Michael Laurence, Sam Minocher Mahaluxmivala, Teja Singh Mangat, Ayub Khan Ommaya, R. A. Roxburgh, Chandramma Dayananda Sagar, Mohyie El-Din Sedky, H. J. K. Vieyra, R. C. W. Williams, Ruth Wynne-Davies, J. G. Allman, R. C. Bennett, D. M. Burgess, G. V. P. Chamberlain, A. C. W. M. Da Roza, J. R. M. Davidson, A. C. B. Dean, Basil Gampel, A. H. Hackett, R. M. Hollings, †L. K. Jobbins, H. R. Johnson, D. M. King, †F. W. Kwock, J. B. Lynch, †R. S. McAlary, J. B. McFarland, Bharat Vrajlal Mehta, Vettivaloo Kandasamy Pillay, D. J. Reid, K. F. Ross, G. B. Smaill, Madho Prashad Vaidya, †I. H. Warner, M. O. Woo-Ming, Soorya Bahadur Basnyat, Suresh Vishvanath Bhave, Cheung-Ping Chan, G. D. Chisholm, Arvind Krishnalal Dangarwala, Arjun Dev, †W. G. Edwards, A. J. J. Emmett, J. I. H. Hadfield, I. M. Hamilton, Leo Lenaghan, F. T. McDermott, M. H. W. Mullerworth, B. F. Reeves, J. S. Scougall, G. A. Syme, D. F. Weinman, Akinpelu Oludele Adesola, Manickavasagar Balasegaram, K. A. Butler, D. M. Essenhigh, H. J. H. Fry, G. R. Gibson, Ann E. Johnson, P. W. B. Lane, †Wilfred Leach, J. B. Morris, E. L. Parry, P. H. Smith.

*In ophthalmology. †In otolaryngology.

At a meeting on June 9, the Lady Cade medal was presented to Group-Captain R. C. Jackson, and the following were co-opted to the council for the year 1960–61, representing various branches of practice:

Mr. T. Keith Lyle, ophthalmology; Mr. C. Gill-Carey, otolaryngology; Mr. H. G. E. Arthure, gynæcology and obstetrics; Dr. G. S. W. Organe, anæsthetics; Prof. M. A. Rushton, dental surgery; Dr. John H. Hunt, general practice; Prof. D. W. Smithers, radiology.

Dr. Preston A. Wade (New York) was appointed second Watson-Jones lecturer. The Mitchiner medal for 1959 was awarded to Lieut.-Col. I. A. Walsh, and for 1960 to Major-General W. D. Hughes. A diploma of fellowship was granted to C. J. Smallwood.

Bequest to Birmingham University

The late Frank Barnes, F.R.C.S., has left the residue of his £137,000 estate to the university "to be used exclusively for or towards the cost of the erection or upkeep or maintenance and improvement of the Medical School, including particularly the library and lecture room".

Royal Australasian College of Physicians

At a meeting of the general body of fellows of the college held in Melbourne on May 25, the following were elected and admitted to fellowship:

Under article 44: F. W. A. Clements, F. C. Courtice (New South Wales); D. O. Shiels (Victoria), Geoffrey Sydney Todd (England). *Under article 42:* B. A. D. Curtin, R. I. Eakin, E. J. Halliday, G. L. McDonald, J. R. Sands (New South Wales); A. V. Jackson, H. I. Jones, L. Murphy, H. P. Taft, H. E. Williams, A. Wynn (Victoria); R. A. Burston, J. S. Covernton, A. K. Grant, R. Hecker, J. M. McPhie (South Australia); P. L. Dorney, F. R. T. Stevens (Tasmania); G. F. Hall, W. J. Smith (New Zealand).

On May 23 the following were admitted to membership:

O. Appenzeller, A. G. G. Bennett, L. Brenner, D. S. Child, J. M. Duggan, N. D. Gallagher, B. Haneman, A. M. Lloyd, M. S. Owen, B. J. Pascoe, R. A. Royle, J. D. Wingfield (New South Wales); H. G. Burger, K. Catt, B. S. Faragher, J. E. Fitzgerald, J. Hansky, A. K. Lethlean, I. G. Lyall, J. F. O'Callaghan, S. F. Phillips, J. G. Sloman, R. R. W. Townley (Victoria); J. T. Andrews, G. T. Ey, A. J. Watson (South Australia); K. R. Hayes, K. P. Kennedy (Queensland); B. R. Beveridge, B. A. Kakulas (Western Australia). *Under article 37:* K. F. Anderson (South Australia); G. M. Watson (New South Wales); Saul Wiener (Victoria).

London Hospital Medical College

On Wednesday, July 13, at 5.15 P.M., at the college hall, Ashfield Street, E.1, Sir Macfarlane Burnet will give the Schorstein lecture. He will speak on the potentialities and limitations of tissue transplantations. Tickets may be had from the secretary of the college, Turner Street, E.1.

Lady Tata Memorial Trust

For research on leukæmia and allied diseases in the year beginning Oct. 1, the trustees have made the following awards:

Grants for research expenses.—Dr. B. M. Braganca (India), Dr. J. Pontén (Sweden), Dr. M. Simonsen (Denmark), Dr. H. J. Woodliff (Great Britain).

Scholarships.—Dr. L. Chieco-Bianchi (Italy), Dr. J. Hastrup (Denmark).

British Medical Association

Dain Fund.—During 1959–60 there was again an increase in the number of applications. A total of 46 cases were helped with grants amounting to £5238. Just under £5000 was received in donations, and the balance in hand at the end of the year was £446. Of the 15 new cases at least 10 are likely to need help for several years, and regular donations to the Fund are welcome.

World Mental Health Year Conference

In connection with World Mental Health Year, a quadripartite conference on community mental health services is to be held on Oct. 7 and 8 at the London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1, between the Central Council for Health Education, the College of General Practitioners, the Royal Medico-Psychological Association, and the Society of Medical Officers of Health. Particulars may be had from the secretary of the society, Tavistock House South, W.C.1.

Hospital Service Plan

The unique circular building which houses the new head offices of the Hospital Service Plan was opened at 157, St. John's Road, Tunbridge Wells, Kent, on May 31 by Sir John Charles, chief medical officer to the Ministry of Health, who commended the Plan as a "self help" organisation. Sir Russell Brain, the chairman, said that the growth of the Plan had necessitated the move from London in search of larger premises.

The Hospital Service Plan enables contributors to provide for private treatment in hospitals or nursing-homes, for specialists' fees, and for other expenses of illness. It is organised by the London Association for Hospital Services and controlled by a council whose members are nominated by the British Medical Association, the three Royal Colleges in London, and King Edward's Hospital Fund for London (its original sponsors), who give their services without remuneration. Commercial, industrial, and professional organisations have taken an increasing interest in it, and in the past five years the membership has more than doubled.

London College of Osteopathy

The Leverhulme Trust Fund is providing scholarships to enable medically qualified men and women to study osteopathy at this college.

These scholarships, valued at £625, will cover the cost of fees and maintenance during the four terms' full-time course which begins next October. Particulars may be had from the secretary of the college, 24, Dorset Square, London, N.W.1.

Mental Health Services Investigation

P.E.P., the independent research organisation, has received a grant of £25,300 from the Nuffield Provincial Hospitals Trust for a study of the mental health services.

The project, which will take three years, will inquire into the future content and pattern of services for the mentally handicapped, with special reference to the possibilities and difficulties of care outside the hospital and will include field studies in selected areas.

Blood-transfusion in Europe

This year the Council of Europe is to use its coordinated medical fellowships for the study of the problems of blood-transfusion in Europe. Three fellows will visit hospitals and blood-transfusion centres in different member countries of the Council and possibly in Switzerland. The research will be carried out under the direction of Dr. J. Spaander, director-general of the Public Health Institute of Utrecht.

Toxic Chemicals in Agriculture

Sir Charles Dodds has been appointed chairman of the Interdepartmental Advisory Committee on Poisonous Substances used in Agriculture and Food Storage, in succession to Sir Solly Zuckerman. The committee was recently reconstituted and its members now include Prof. J. H. Gaddum and Prof. Andrew Wilson.

A Regional Course in Psychotherapy

The North East Metropolitan Regional Hospital Board has approved a scheme for instruction in psychotherapy for doctors who are being trained in the region.

Courses of twelve weekly seminars will be held at the Institute of Psychiatry, the Maudsley Hospital, by a senior staff member. Each course will be limited to 8 doctors. The board will reimburse the fees and travelling expenses to 8 selected candidates in the grades of registrar, senior registrar, and junior hospital medical officer. Senior hospital medical officers and consultants will be expected to pay their own fees and expenses. The first course began on May 4.

Psychosomatic Medicine and Childbirth

An international congress on this subject will be held from Sept. 12 to 15, 1961.

It has not been finally decided where this meeting will take place, but the most likely places are Paris, Vienna, or Geneva. The subjects chosen for discussion are psychological and sociological study of the woman in connection with her pregnancy, labour, and the puerperium; psychophysiology of the pain of labour; theory, practice, and results of combined psychological and physical preparation for labour; and the value and the limitations of the psychosomatic methods in obstetrics. Those who wish to contribute are asked to get in touch with Prof. Norman Morris, Charing Cross Hospital Medical School, London, W.C.2.

Teratology Society

For several years anatomists, biochemists, embryologists, geneticists, obstetricians, pathologists, pediatricians, plastic surgeons, and other scientists have held informal conferences on basic problems of congenital malformations, and after the fourth teratology conference, held at the Memorial Sloan-Kettering Cancer Center in New York City and attended by 76 scientists from Canada, England, France, Germany, and the United States, it was decided to form a society to hold regular meetings in which investigations into the ætiology and morphogenesis of congenital malformations could be presented and discussed. Prof. Josef Warkany was elected president and Dr. Marjorie M. Nelson secretary-treasurer. Her address is department of anatomy, School of Medicine, University of California, San Francisco 22.

Royal Institute of Public Health and Hygiene

Dr. W. A. R. Thomson will give the Bengué lecture on Wednesday, Oct. 19, at 5 P.M., at the institute, 28, Portland Place, London, W.1. His subject will be Doctors, Drugs, and Diseases.

On Friday, July 8, at 8 P.M. at the Midland Centre for Neurosurgery, Holly Lane, Smethwick, nr. Birmingham, Dr. A. Huber of Zürich, will give a lecture on eye symptoms in brain tumours.

On Tuesday, July 19, at 5.30 P.M., at St. Mary Abbots Hospital, Marloes Road, Kensington, W.8, Dr. James Arnhoff, of the Mount Sinai Hospital, New York, will give a lecture on psychosomatic E.N.T. problems.

Under the chairmanship of Prof. A. V. Neale, a joint committee of the Bristol division of the British Medical Association and the Bristol local medical committee have been studying "the prevention of break-up families". Copies of their report (5*s.* 6*d.*, post free) may be had from the local medical committee, 7, the Dell, Westbury-on-Trym, Bristol.

Practical Dietetics—The series of articles which appeared under this title during 1959 in *The Practitioner* (5, Bentinck Street, London, W.1) have now been reprinted as a booklet (4*s.* 6*d.*) under the editorship of Dr. W. A. R. Thomson.

The Cambridge Graduates' Medical Club will hold its annual general meeting and dinner at Pembroke College on Friday, July 1. Members who have not yet received notification, or other Cambridge men interested, should write immediately to H. E. Batten, F.R.C.S., 67, Bridge Street, Cambridge.

Diary of the Week

JUNE 19 TO 25

Monday, 20th

UNIVERSITY OF LONDON
5 P.M. (University College Hospital Medical School, University Street, W.C.1.) Prof. N. C. Louros (Athens): Reduction of Pain During Labour and Delivery.

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. Brian Ackner: Anorexia Nervosa.

Tuesday, 21st

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Dr. J. G. Scadding: Mycobacterium Tuberculosis in the Ætiology of Sarcoidosis. (Mitchell lecture.)

UNIVERSITY OF LONDON
5 P.M. (London Hospital Medical College, Turner Street, E.1.) Dr. Austin T. Moore (Columbia, South Carolina): Surgery of the Hip with Special Reference to Moore Arthroplasty.

Wednesday, 22nd

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Miss Jessie Dobson: A Hitherto Undescribed Section of John Hunter's Museum. (Arnott demonstration.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Prof. S. D. Elek: Cytomegalic Inclusion Body Disease.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. R. W. Riddell: Infections Due to Yeasts.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. S. W. A. Kuper: B.C.G. Vaccination and Leprosy.

ROYAL COLLEGE OF SURGEONS OF EDINBURGH, Edinburgh, 8
5 P.M. Prof. Robert B. Duthie (New York): Histochemistry of Bone Repair.

Thursday, 23rd

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
2.30 P.M. *Urology.* Mr. W. T. Irvine, Mr. J. B. Yule, Mr. D. G. Arnott: Absorption of Electrolytes Across a Colonic Mucosa. Prof. L. N. Pyrah: Transplantation of the Ureters into an Isolated Rectum. Sir Eric Riches: Colo-cystoplasty. Mr. Richard Turner-Warwick: Colonic Conduits.

POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. R. J. G. Sinclair: The Marfan Syndrome.

INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W.C.1
5 P.M. Dr. Edith L. Potter (Chicago): Perinatal Mortality Studies at the Chicago Lying-in Hospital.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Brian Russell: Uncommon Skin Tumours, Clinical and Pathological.

BRITISH ASSOCIATION OF UROLOGICAL SURGEONS HOME AND OVERSEAS
9.30 A.M. (Royal College of Surgeons of England.) Opening of two-day meeting.

Friday, 24th

ROYAL SOCIETY OF MEDICINE
8.15 P.M. *Obstetrics & Gynæcology.* Professor Louros, Mr. H. P. White, Dr. D. W. Warrell, Mr. C. A. Simmons: Urinary Incontinence in Women.

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Dr. G. W. Taylor: Primary Lymphœdema.